From
THE DEPARTMENT OF MOLECULAR MEDICINE AND SURGERY
Karolinska Institutet, Stockholm, Sweden

COMPLICATIONS FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Stockholm 2021

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Published by Karolinska Institutet
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-120-6
Cover illustration and illustrations page 5 and 8 by Elin Kurtsdotter

Complications following anterior cruciate ligament reconstruction
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public in Ejnarsalen, Sophiahemmet, Stockholm, on 12 March 2021, at 09.00 AM

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To the best family

POPULAR SCIENCE SUMMARY OF THE THESIS

Two feared complications following anterior cruciate ligament (ACL) surgery are blood clots in the venous bloodstream and infections in the joint; venous thromboembolism and septic arthritis. Thromboembolism is most common in the lower leg, but it can propagate and enter into the lung circulation, a life-threatening condition in which cardiac arrest can occur. Septic arthritis is normally caused by bacteria. The infection can lead to damage to the cartilage, with poorer function in the affected joint. These serious complications are rare and difficult to study. Using register data, this thesis establishes their occurrence and presents novel risk factors.

The ACL is a knee ligament with the function of stabilising the knee. It can be injured during sports participation, such as soccer or alpine skiing. Once injured, the ACL does not heal and entails an increased risk of osteoarthritis of the knee. The treatment is dependent on the patient's need and the degree of knee instability, and consists of rehabilitation with or without surgery. The torn ACL is replaced during surgery using a tendon, which is most frequently harvested from the patient itself.

The patient undergoing surgery is often young (mean age 27 years), active and working actively to return to the same activity level as before the injury. In Sweden, approximately 4,000 surgeries of the ACL are performed each year.

This thesis is based on register data and includes more than 25,000 patients. By combining different sources of register data, it is possible to present a reliable number of the complications, as well as their risk factors. Using patient questionnaires, the outcome after surgery for patients with and without the complications can be measured.

The studies in this thesis have shown that venous thromboembolism occurs in 0.4% of the surgeries, while the corresponding number for septic arthritis is 1.1%. Identified non-modifiable risk factors include, for venous thromboembolism, age at surgery and, for septic arthritis, sex. Modifiable risk factors for septic arthritis include the choice of tendon to replace the torn ACL, the choice of antibiotics administered at the time of surgery and the duration of surgery. The outcome for patients with postoperative venous thromboembolism and septic arthritis was poorer compared with patients without infection.

With the knowledge of the presented risk factors in this thesis, it is possible to reduce the number of complications, and to improve the care and outcome of patients with ACL injuries.

ABSTRACT

Background: Venous thromboembolism (VTE) and septic arthritis (SA) are two rare complications following anterior cruciate ligament reconstruction (ACLR). Due to their rare incidence, risk factors and outcome are difficult to analyse and the aims of this thesis are to improve knowledge in this area.

Methods: All studies are register based. The study populations have been extracted from the Swedish Knee Ligament Register (SKLR) and have been linked to data from registers at the National Board of Health and Welfare to establish the incidence. A nationwide medical record review was performed to verify the events of SA. Risk factor analyses were made with data from both register sources. The subjective outcome was initially investigated with a non-response analysis of the SKLR, including a separate non-response questionnaire. Secondly, the subjective outcome for patients with VTE and SA was analysed based on data extracted from the SKLR. Finally, the risk of revision ACLR was investigated among patients with SA after primary ACLR.

Results: The incidence of VTE and SA after ACLR was 0.4% and 1.1% respectively. The analyses of risk factors revealed that older age at surgery is the only independent risk factor for VTE after ACLR; while male sex, longer operating time, use of clindamycin instead of cloxacillin and a hamstring tendon autograft instead of a patellar tendon autograft are independent risk factors for SA after ACLR.

The response rate for the subjective outcome is higher among female and older patients, with small differences in the outcome scores between respondents and non-respondents.

The patients with SA report an inferior subjective outcome on all follow-up occasions and a poorer long-term outcome. The risk of revision ACLR is doubled among patients with SA after primary ACLR compared with patients without SA.

Conclusion: This thesis demonstrates that an analysis of rare complications is possible using register data. Novel findings relating to risk factors for the studied complications, as well as novel findings on outcome data for patients with SA after primary ACLR, are presented. Knowledge about the risk factors can be used to modify and optimize perioperative routines in order to decrease the risk of serious complications and revision surgery, and to increase the subjective outcome after ACLR.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **A non-response analysis of 2-year data in the Swedish Knee Ligament Register**
John Reinholdsson, Jesper Kraus Schmitz, Magnus Forssblad, Gunnar Edman, Martina Byttner, Anders Stålman
Knee Surgery, Sports Traumatology, Arthroscopy, 2017Aug; 25(8): 2481-2487

II. **Deep venous thrombosis and pulmonary embolism after anterior cruciate ligament reconstruction: incidence, outcome and risk factors**
Jesper Kraus Schmitz, Viktor Lindgren, Per-Mats Janarv, Magnus Forssblad, Anders Stålman
The Bone & Joint Journal, 2019 Jan; 101-B(1): 34-40

III. **Risk factors for septic arthritis after anterior cruciate ligament reconstruction: a nationwide analysis of 26,014 ACL reconstructions**
Jesper Kraus Schmitz, Viktor Lindgren, Gunnar Edman, Per-Mats Janarv, Magnus Forssblad, Anders Stålman
The American Journal of Sports Medicine, 2021; accepted for publication

IV. **Septic arthritis has an effect on the subjective outcome and the risk of revision following anterior cruciate ligament reconstruction: a register-based cohort study on 23,075 primary ACL reconstructions**
Jesper Kraus Schmitz, Osama Omar, Adam Lennartsson, Henrik Hedevik, Per-Mats Janarv, Anders Stålman
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
ADL	Activity of daily life
ATC	Anatomical therapeutic chemical
CDR	Causes of death register
CI	Confidence interval
DVT	Deep vein thrombosis
EQ-5D	The European quality of life five dimension
ICD	International classification of diseases
I&D	Irrigation and debridement
KOOS	Knee injury and osteoarthritis outcome score
MRI	Magnetic resonance imaging
NPR	National patient register
OR	Odds ratio
PCL	Posterior cruciate ligament
PE	Pulmonary embolism
PIN	Personal identification number
PROM	Patient-reported outcome measure
QoL	Knee-related quality of life
SA	Septic arthritis
SD	Standard deviation
SKLR	Swedish knee ligament register
SPDR	Swedish prescribed drugs register
VTE	Venous thromboembolism

1 LITERATURE REVIEW

1.1 HISTORY OF ANTERIOR CRUCIATE LIGAMENT

The anterior cruciate ligament (ACL) is a thoroughly studied ligament located in the central part of the knee. The ACL was first mentioned by Galen of Pergamon (131-201 AD), a greek physician who named the two cruciate ligaments based on their crossing appearance "ligamenta genu cruciata". During the following 2000 years, the ACL was paid little documented attention. It is first in 1836 that the two brothers, Wilhelm and Eduard Weber, professors of Physics and Anatomy and Physiology in Leipzig, demonstrated the abnormal anterior-posterior movement of the tibia following sectioning of the ACL – the first described anterior drawer sign. In 1845, the french surgeon Amedeé Bonnet described three signs indicating an ACL rupture: "In patients who have note suffered a fracture, a snapping noise, haemarthrosis, and loss of knee function…". He was also one of the first surgeons to describe the pivot-shift test: a subluxation is provoked in the ACL deficient knee. Another common test to diagnose the ACL injury is the Lachman test, which was described by the greek surgeon Georgios C. Noulis in 1875. However, the name Lachman orginates from the orthopaedic surgeon John Lachman who was active in Philadelphia, US, during the second half of the 20th century (1).

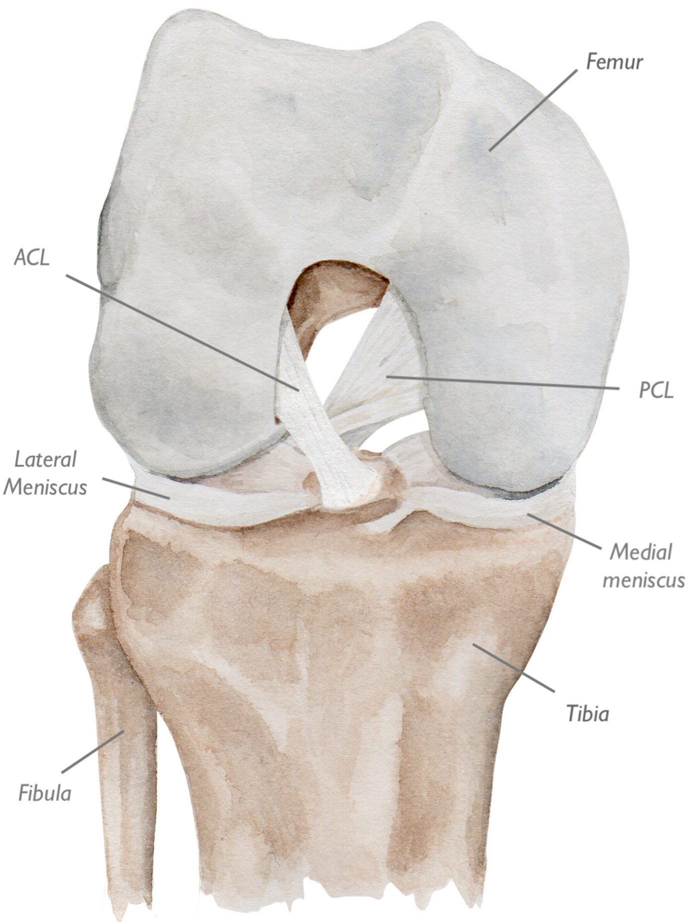

Figure 1. Anatomy of a right knee with patella removed.

1.2 ANATOMY OF THE KNEE

The knee joint consist of four bones: the femur, tibia, fibula and patella. Several muscles with their tendon insertions, the menisci and ligaments interact to stabilise the knee. The central part of the knee has two cruciate ligaments, the ACL and the posterior cruciate ligament (PCL) (2) (Figure 1).

The ACL is composed of type 1 collagen fibres and its blood supply derives mainly from the middle geniculate artery. The ligament is surrounded by synovial tissue which also contributes to the metabolism (3, 4).

The ACL originates from the lateral femoral condyle notch in a ribbon-like structure with the lateral intercondylar ridge, as the anterior border, and the articular surface, as the posterior border (5). The insertion on the tibial eminence is duck foot-like or c-shaped with the bony landmarks "Parsons's knob" anteriorly, the intertubercle ridge posteriorly and the medial intercondylar ridge medially (6). The largest cross-sectional area of the ACL is at the tibial insertion with 175 mm^2, followed by the femoral insertion with 122 mm^2, while the smallest area is found in the mid-substance with 40 mm^2 (7).

The main functions of the ACL are to balance and stabilise the knee in both the anterior-posterior and the rotational plane (2). Different parts of the ACL act, with varying tension, during the range of motion of the knee, and were functionally divided into two bundles, the anteromedial (AM) and the posterolateral (PL), named after their insertions on the tibial side. The AM bundle is moderately lax when the knee is extended and tightens when the knee is flexed. The opposite applies to the PL bundle. In this way, the separate bundles counteract to stabilise the knee joint throughout the range of motion (8, 9). The length of the ACL varies from 24 mm, in an unloaded 90-degree position of the knee joint, and 31 mm, when the knee is fully extended and an anterior tibial translation load is applied to the knee (7).

1.3 EPIDEMIOLOGY

The incidence of cruciate ligament injury in Sweden is 78/100,000 person-years (10). The corresponding number in the United States is uncertain, but it is estimated that around 200,000 ACL injuries occur yearly (11). In the Swedish population, the mean age at which a cruciate ligament injury is sustained is 32 years, with 60% males. In younger patients, 11-20 years, females are injured to a greater extent than males (10).

1.4 AETIOLOGY

The ACL is exposed to a possible injury or tear during cutting and pivoting movements which can occur in daily life but more specifically during sports participation. In Sweden, the top three causes of ACL injury are soccer, alpine skiing and team handball (12).

Most of the ACL injuries occur without contact with another person. The tear is considered to be caused by a deceleration combined with a change of direction, or following a jump where the landing takes place with the knee in or near full extension (13, 14).

The risk factors for an ACL injury are multifactorial and can be divided into environmental (weather, footwear), anatomical (BMI, femoral notch, knee recurvatum, joint laxity), hormonal (sex, menstrual status), neuromuscular (balance between muscles around the knee, trunk proprioception) and biomechanical (balance between the trunk and joints in the lower extremities) (15).

1.5 DIAGNOSIS

The diagnosis of an acute ACL injury is based on a combination of the patient's history, which often includes some kind of popping sensation at the time of the injury, followed by a rapid effusion in the knee joint, and a thorough physical examination (16). The physical examination should include the Lachman and the pivot shift test. In a review, their respective sensitivity has been estimated at 85% and 30-40% and their specificity at 94% and 98% (17). Magnetic resonance imaging (MRI) can be used to diagnose the ACL tear, as well as concomitant injuries (18)(Figure 2). In a review compromising only prospective studies, the sensitivity and specificity of the MRI on ACL tears have been estimated at 87% and 93% respectively (19).

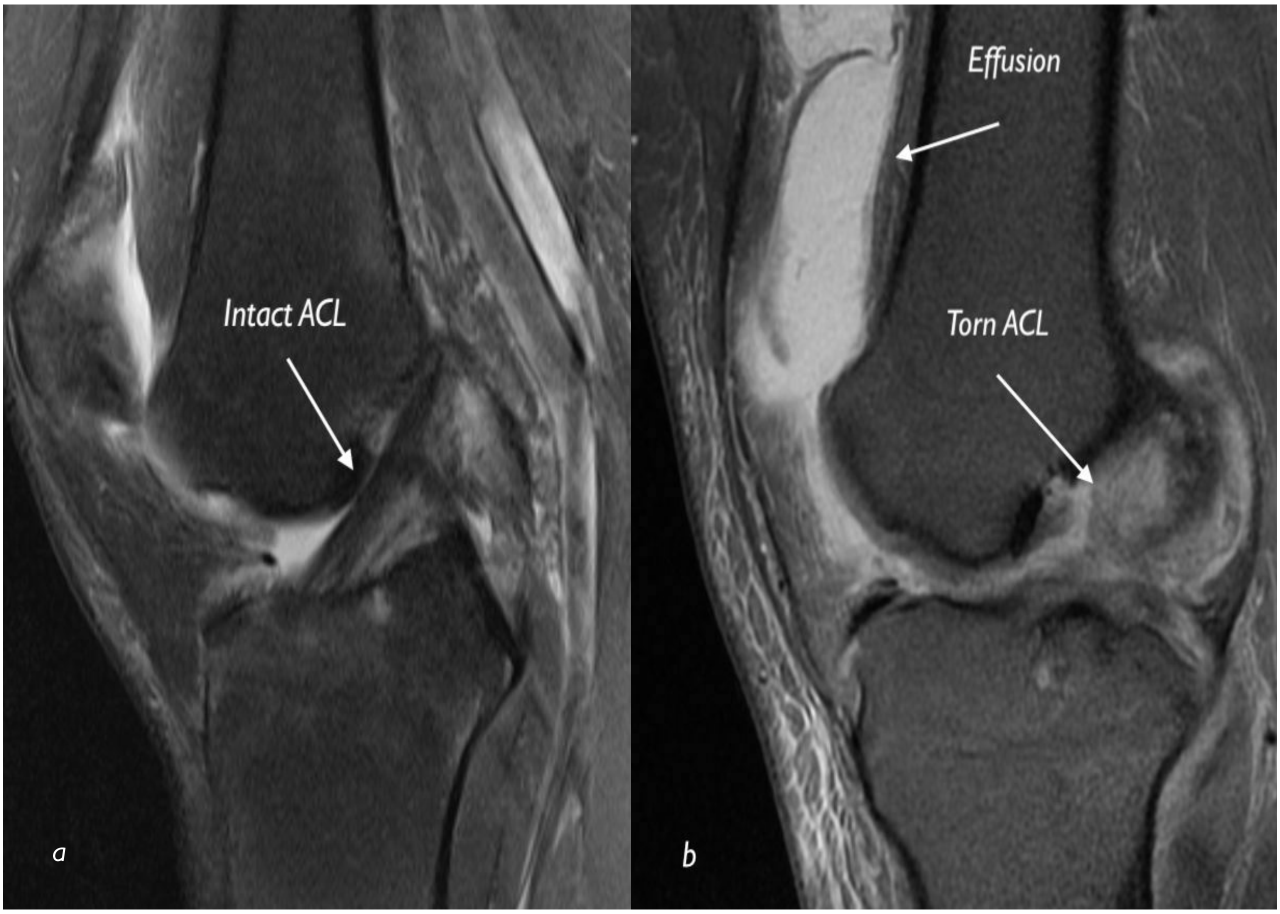

Figure 2. MRI with sagittal view displaying a) knee with intact ACL, b) knee with torn ACL and effusion.

1.6 TREATMENT

The treatment of an ACL injury can be categorised into two entities; surgical and non-surgical. Surgery is recommended to patients with high knee stability demands in their occupation, or if the patient participate in a sport, with a high demand for knee stability. Surgery can sometimes also be indicated if the patient experience subjective instability in activities of daily living. Where the demands on knee stability are uncertain, an initial rehabilitation period, followed by an evaluation of function and subjective knee stability, can be advocated. If the patient has severe instability and/or episodes of "giving-way" following the rehabilitation period, surgery is usually recommended (16, 20, 21). By monitoring the patients during the rehabilitation period, it is possible to identify those in need for additional rehab or surgery, and to reduce the risk of associated injuries to the menisci and cartilage, which might lead to long-term poor results and osteoarthritis (22).

Approximately half of all ACL injuries in Sweden are treated with surgery and the mean age of patients undergoing surgery is 28 years (21).

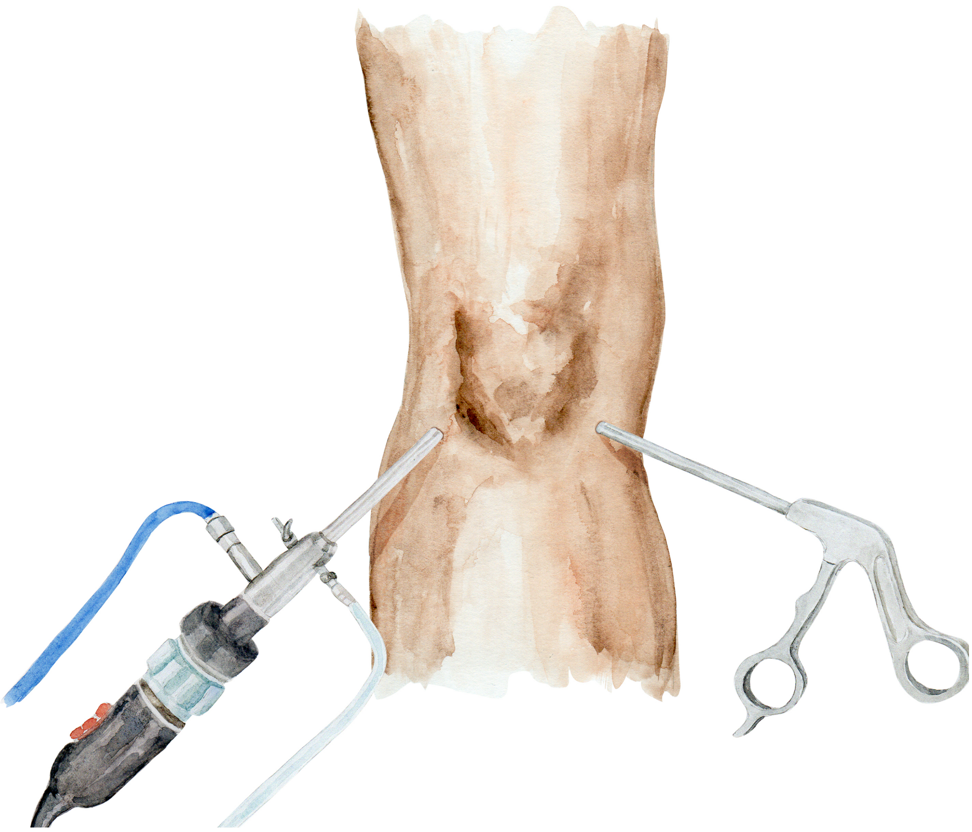

Figure 3. Illustration of a right knee with the arthroscopic camera through the anterolateral portal and the arthroscopic forceps through the anteromedial portal.

1.6.1 ACL repair

The first described surgery was in 1895 when Sir Arthur Mayo-Robson performed an open ACL repair with silk sutures. The technique developed during the 20th century, but, in the end, it was finally abandoned due to poor results (1). In recent years, promising results have been reported and the technique is perhaps regaining its place, especially when the blood supply to the ACL is considered with only proximal tears being repaired. The technique often involves some kind of augmentation and it is thus considered more intricate to perform. However, it is still considered highly controversial with a lack of long-term outcome data (23, 24).

1.6.2 ACL reconstruction

1.6.2.1 History

Parallel to ACL repair, the technique of ACL reconstruction (ACLR) evolved and, in 1917, Ernest William Hey Groves in Bristol performed the first ACLR using the fascia lata as a graft. The second graft to be used was the meniscus, which was followed by the use of patellar, quadriceps and hamstring tendons. These three tendon grafts are still in use today. Open surgery has currently been abandoned after the development of arthroscopic surgery. In 1912, the Danish surgeon, Severin Nordentoft, presented the use of an endoscopic technique to a joint – arthroscopy – and the first arthroscopically assisted ACLR was performed by David Dandy in Newmarket, UK, in 1980 (1, 25)(Figure 3).

1.6.2.2 Surgical technique

Different techniques for performing the arthroscopic drilling have evolved since 1980. Initially, the surgery was performed with the aim of placing the graft isometrically, often using a transtibial technique. Today, an ACLR is perfomerd by placing the graft anatomically, i.e. at the origin and insertion of the native ACL, and using three portals (26)(Figure 4a-c).

1.6.2.3 Graft choice

The choice of graft is an important aspect of ACLR. In Sweden, the most commonly used graft is a hamstring tendon autograft which consists of either the semitendinosus tendon together with the gracilis tendon, both doubled, or a quadrupled semitendinosus tendon (Figure 6). Another option is the patellar tendon autograft, which is harvested with bone blocks from both the patella and the tuberositas tibiae. With bone blocks, the healing and incorporation in the drilled tunnels is better than with soft-tissue grafts (27, 28). Soft-tissue grafts typically need 8-12 weeks to fully heal into the tunnels, followed by a remodelling process lasting at least 12 months (29-31). In Sweden, the patellar tendon autograft was the most commonly used graft until the beginning of the 21st century when hamstring autografts rapidly became more popular. Today, hamstring autografts are used in 85% of the ACLRs in Sweden (21). The reasons for the popularity of the hamstring tendon autograft could be the relatively easy harvesting and low donor-site morbidity.

Many studies report more donor-site morbidity, due mainly to anterior knee pain with patellar tendon autografts during the first two years after ACLR (32).

In studies comparing patellar with hamstring tendon autografts, the patient-reported outcome is similar or slightly better for the hamstring autograft in the short-term follow-up, with the potential drawback of an increased risk of revision ACLR compared with patellar tendon autografts (33, 34). Another proposed disadvantage of soft-tissue grafts is the risk of tunnel widening, which can complicate surgery if a revision is needed (35).

The quadriceps tendon autograft is a third graft option, which is used less frequently but with increasing popularity. It can be harvested with or without bone blocks from the patella and is currently used in 6% of the ACLRs in Sweden (21, 36), increasing from low numbers. A recent prospective trial reported a similar patient-reported outcome and objective knee stability, when comparing quadriceps and hamstring tendon autografts, and the patients with quadriceps tendons had less donor-site morbidity but inferior quadriceps strength at the one-year follow-up (37).

Finally, there is the option of using allografts with the benefits of no donor-site morbidity and reduced surgical time but the possible drawbacks of poorer healing, inferior mechanical properties and higher costs. The tissues that are used include the tibialis posterior, tibialis anterior, Achilles and patellar tendons. The allograft is recommended to be fresh frozen and not prepared with irradiation or a chemical process, which adversely can affect the graft properties (38). However, The use in Scandinavia is limited, with less than 1% in Sweden, whereas its use in the United States is around 20% (21, 39).

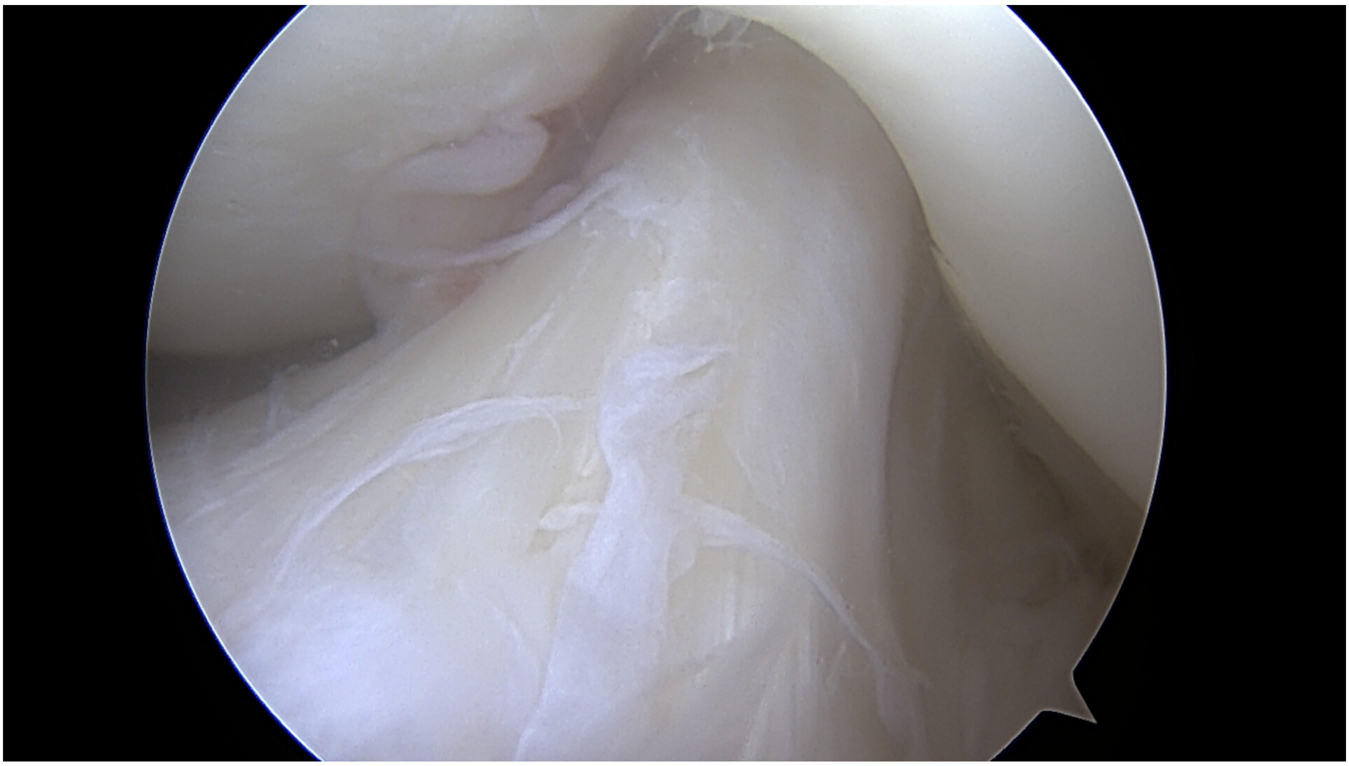

Figure 4a. Arthroscopic view of a left knee with an intact ACL.

Anatomically individualised ACLRs are a growing concept which, for example, includes graft choice based on the patient's needs and requirements (40). However, when comparing the graft choice between countries, with 64% patellar tendon autografts in Norway and 8% in Sweden, it is obvious that there are differences in routines and traditions in the choice of graft between countries, that cannot be explained with graft choice due to patient related factors (21, 41).

1.6.2.4 Epidemiology

In 2019, 3,951 primary ACLRs were performed in Sweden (21). The corresponding number in the United States is more uncertain, but 129,836 ACLRs were reported in 2006 (11). The mean age of patients undergoing ACLR in Sweden is 27, while it is 29 in the United States. The proportion of female patients is 46% in Sweden and 42% in the United States (11, 21).

1.7 PATIENT-REPORTED OUTCOME MEASURES

Patient-reported outcome is one important way of measuring the effect of a given treatment. Normally, the patient-reported outcome measure (PROM) consists of a self-administered questionnaire. To best evaluate the effect of a treatment, it is recommended that a combination of a generic- and a disease-specific measurement should be used (42).

1.7.1 European Quality of Life Five Dimension

The European Quality of Life Five Dimension is a two-page questionnaire where the respondents describe their current health state. The first page includes five questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question has a three-level scale ranging from "no problems" to "extreme/severe problems". An index value from 0 (worst) to 1 (best) is then calculated from the responses. The final page of the questionnaire includes a visual analogue scale (VAS) where the respondents grade their current state of health on a scale from 0-100, where 0 is the worst imaginable health state and 100 the best imaginable health state (43).

1.7.2 Knee injury and Osteoarthritis Outcome Score

In 1995, the Knee injury and Osteoarthritis Outcome Score (KOOS), was developed from the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, to assess the outcome in patients with ACL injuries and osteoarthritis. It consists of five subscales: Symptoms, Pain, Activity of Daily Life (ADL), Sport and recreational function and Knee-related Quality of Life (QoL). Each subscale has several questions, to which the patient gives a score on a five-point Likert scale[1]. The results are transformed to a 0-100 scale for each dimension, where 100 represents no knee problems (44, 45).

[1] Likert scale – scale where the respondent answers a question on a five- or seven-point scale, named after the psychologist Rensis Likert

1.7.3 Minimal Important Change

The minimal important change is the smallest change in a PROM score, which can measure a clinical difference (46). It has been suggested that a KOOS difference over time of 8-10 points indicates a clinical difference (47). In a more recent publication based on anchor questions, it is shown that the KOOS subscales of Sport and recreational function and QoL are preferred as primary outcomes with minimal important change values of 12.1 and 18.3 respectively. The subscales of Symptoms, Pain and ADL are not considered useful when analysing within-group change over time (48).

1.7.4 Response rate

One problem when collecting follow-up data is poor compliance and non-response. Historically, a response rate of 60% has been regarded as acceptable. However, this threshold has no scientific support and analysing the non-response group is instead recommended. If the non-response group does not differ that much from the response group, a lower response rate could be acceptable and vice versa (49).

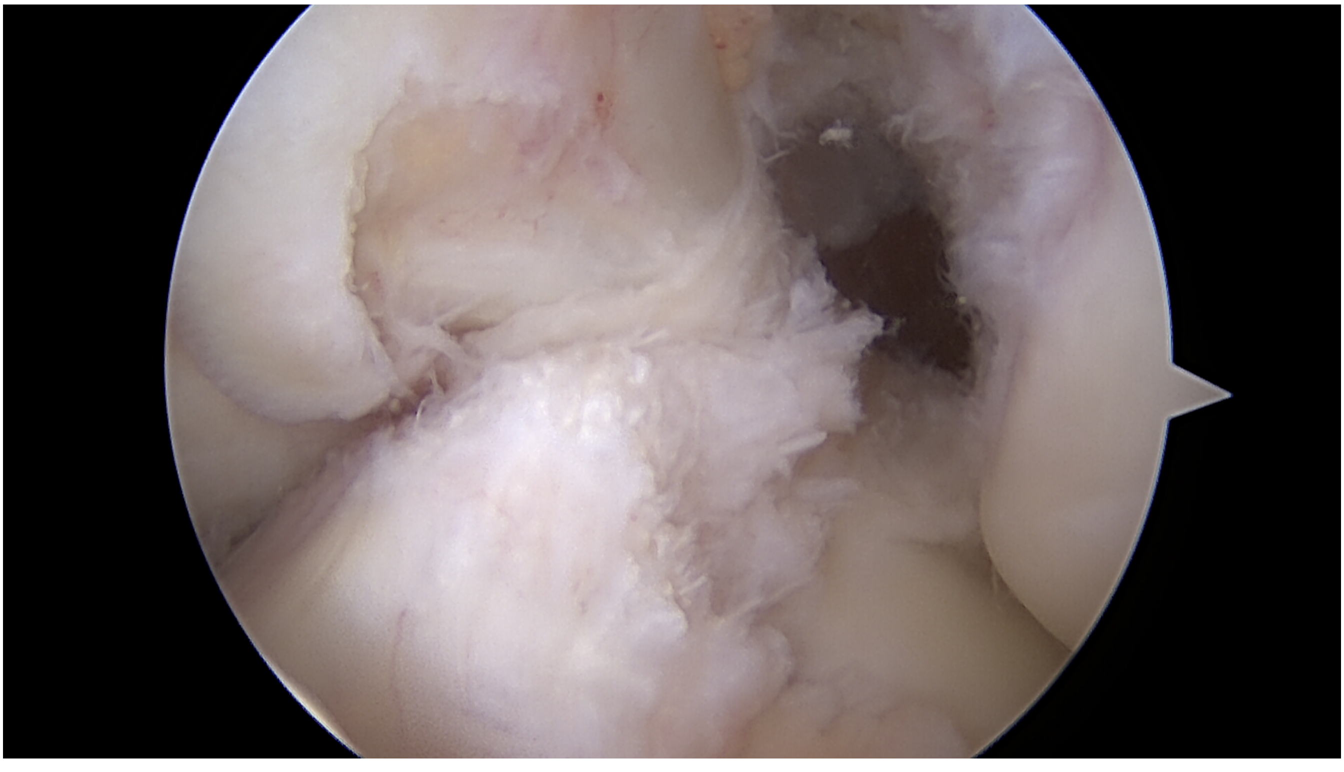

Figure 4b. Arthroscopic view of a left knee with a torn ACL.

1.8 REGISTERS

Together with the other Nordic countries, Sweden has a long tradition of using registers. There are two categories of registers in Sweden; national public authority registers that are established via the Swedish Parliament and include all individuals without the opportunity to opt out. The health data registers at the National Board of Health and Welfare and the Population Register at Statistics Sweden are two examples. The other category is the national quality registers where the majority have been initiated by healthcare professionals. The quality registers include specific and more detailed information regarding the disease and/or treatment, normally together with a section with patient-reported outcome. In contrast to the public authority registers, the patient registers include an opportunity to opt out (50, 51).

Two important terms when analysing a register are completeness and coverage. Completeness refers to the degree to which the register includes eligible patients among the target population. Coverage refers to the extent to which the number of units that are participating in the register among all the existing units perform data collection (50).

1.8.1 The Personal Identification Number

The personal identification number (PIN) is a unique identifier for each individual in the Swedish Population Register. It consists of date of birth, a three-digit birth code and a check digit and was introduced in its present form in 1967. Today, the Swedish Tax Agency is responsible for the administration of the PIN (52). The PIN makes analysis between different registers possible.

1.8.2 The National Patient Register

The National Patient Register (NPR) is administered by the Swedish National Board of Health and Welfare. The register was started in the 1960s and, since 2001, it has included all in- and out-patient care in Sweden excluding primary health care. It consists of patient data (PIN, sex, age, place of residence), geographical data (hospital), administrative data (date of admission/discharge) and medical data (main and secondary diagnosis, procedures). Diagnoses are coded according to International Classification of Diseases (ICD) version 10 (53, 54).

1.8.3 The Swedish Prescribed Drugs Register

The Swedish Prescribed Drugs Register (SPDR) was started in July 2005 and includes all dispensed drugs. It consists of patient data (PIN, sex, age, place of residence), drug data (name, dose, dispensed amount) and administrative data (date of prescription and dispensing, profession and practice of the prescriber). The drugs are classified based on the Anatomical Therapeutic Chemical (ATC) classification system (55, 56).

1.8.4 The Causes of Death Register

The Causes of Death Register (CDR) was started in 1961 and includes all deaths and causes of death in Sweden (57).

1.8.5 The Swedish Knee Ligament Register

The Swedish Knee Ligament Register (SKLR) is a quality register established in 2005 (Figure 5). It has completeness of more than 90% of all ACLRs in Sweden. The register consists of two parts: reports and perioperative observations by the surgeon, e.g. associated intra-articular injuries, type of graft, thrombo- and antibiotic prophylaxis administered and patient self-reported data. The patients register baseline data (BMI, smoking), the KOOS and the EQ-5D. The KOOS and EQ-5D are registered preoperatively and at one, two, five and 10 years postoperatively. The response rates in the SKLR in 2012 were 60% and 52% for the one- and two-year KOOS follow-ups, with even lower rates for the EQ-5D. In recent years, the response rate has declined (21, 58).

1.9 COMPLICATIONS

1.9.1 Venous thromboembolism

Thrombosis is the occurrence of a clot in a blood vessel. It can be both arterial and venous, where the most common are clots that occur in arterial vessels which can cause a myocardial infarction or stroke. When the clot occurs in a vein, it is called a venous thromboembolism (VTE). Most commonly, a clot is formed in the calf as a deep vein thrombosis (DVT) which can either resolve spontaneously or propagate proximally (59). When the thrombosis enters the pulmonary circulatory system, it is called a pulmonary embolism (PE). The PE affects the cardiac workload to various degrees and, in the worst case, causes cardiac arrest and death (60).

Another possible consequence of a DVT is the post-thrombotic syndrome, which is a chronic condition with a wide spectrum of symptoms from a swollen and painful extremity to severe leg ulcers. It is estimated that between 20-50% of the patients with a DVT develop post-thrombotic syndrome (61).

1.9.1.1 Virchow's Triad

During the 19th century, Rudolf Virchow's work on the way a venous thrombosis is formed resulted in the concept of "Virchow's triad", which is still applied today, where at least one in three underlying factors can cause a thrombosis (62, 63).

- Δ Abnormalities of the vessel wall. Trauma can cause an injury to the vessel wall, which causes a reduction in the anticoagulants produced by the endothelium (60, 64) and in turn causes a state of hypercoagulability.
- Δ Abnormalities of the blood constituents. Obesity, pregnancy, cancer and oral contraceptives are examples where the blood coagulation cascade per se is affected and causes a state of hypercoagulability (64).
- Δ Abnormalities of the blood flow. Reduced blood flow caused by stasis or immobility. Examples are long travel distances and postoperative immobilisation. The reduced circulation causes an imbalance between the factors in the anticoagulant pathway and the factors that coagulate the blood, in favour of the latter (64).

Figure 5. The Swedish Knee Ligament Register annual reports from 2008 to 2019.

1.9.1.2 Incidence and risk factors

In the general population, the incidence of VTE is estimated at 100 per 100,000 person-years and, of these, approximately 30% are PE (65). The mean age of VTE, in an adult population from northern Sweden (county of Västerbotten), is 73 years for women and 68 years for men (66). There are several known general risk factors for VTE, including age, genetic factors, cancer, immobilisation, trauma and surgery (65). In a ten-year report on 45,698 orthopaedic procedures from one institution, the overall incidence of VTE was 1.1%, with a distribution from 0.2% (upper extremity surgery) to 12% (internal fixation after pelvic fracture)(67).

Following ACLR, the incidence of VTE varies with the type of study and whether asymptomatic and symptomatic VTE has been analysed. In register-based studies analysing symptomatic VTE, the incidence is reported as between 0.16% and 0.53% (68-70). In contrast, the incidence is 9% to 14% when asymptomatic VTE is analysed (71, 72). Most of the studies of VTE following ACLR are based on small cohorts with limited information on comorbidity and risk factors. However, some risk factors in the ACLR setting have been established; older age (69, 70, 73), tourniquet use > 120 minutes (74), multi-ligament reconstruction (70, 71), operating time > 90 minutes (73) and female sex (73).

Figure 6. Quadrupled semitendinosus autograft

1.9.1.3 Thromboprophylaxis

To prevent postoperative VTE, recommendations from the American College of Chest Physicians on when to use thromboprophylaxis have been established. However, these recommendations only apply to arthroplasty and arthroscopic surgery in general and not specifically to patients undergoing ACLR (75). In a survey of Swedish ACL surgeons, 82% prescribed thromboprophylaxis when risk factors such as a history of thrombosis and oral contraceptives were present (76).

1.9.2 Septic arthritis

Septic arthritis (SA) is when a joint is infected by a microorganism, most commonly bacteria (77). In native joints, the most common path of transmission is hematogenous and it is thought that the microorganism enters the joint through the synovium which is vulnerable due to the lack of a protective basement membrane (78). The top three groups of bacteria causing native SA are Staphylococci, Streptococci and Gram-negative rods (79). Presumably, all joints can be affected by SA, and the most frequently involved joint among adults is the knee (78). In children, the hip joint is more frequently involved (80).

The infected joint is damaged by three mechanisms; toxin produced by the bacteria, host inflammation response with the release of collagen-degrading enzymes and joint asphyxia caused by high intra-articular pressure (81).

1.9.2.1 Incidence and risk factors

The incidence of SA in the general population is 2-10/100,000 person-years (77, 80) and general risk factors for SA are pre-existing joint disease (rheumatoid arthritis, gout, osteoarthritis), diabetes mellitus, cirrhosis, end-stage renal disease and prednisone and other immune-suppressive medications (78).

Deep infection following total hip arthroplasty surgery ranges from 0.3% to 0.9% and the corresponding figure for total knee arthroplasty is 0.9% to 1.1% (82-84). Following ACLR, the rate of SA, in register-based cohorts, is reported as ranging from 0.28% to 1.0% (85, 86). Studies from single institutions show a higher rate from 0.58% to 1.8% (87, 88). The most common pathogen for SA after ACLR is coagulase-negative staphylococcus (89).

The risk factors presented for SA after ACLR are diabetes mellitus (90), smoking (86), inpatient surgery (85) and hamstring autografts (88). However, bias can be attributed to theses analyses, as the cohorts are mostly of small size and the incidence rate is low.

1.9.2.2 Treatment of SA following ACLR

The initial treatment of SA following ACLR is to perform immediate arthroscopically assisted irrigation and debridement (I&D), with the retrieval of cultures as biopsy specimens, irrigation of the joint with 10-15 litres of saline solution and the initiation of empirical antibiotic treatment (91, 92). There are conflicting recommendations on whether to preserve or remove the graft (93) and in Sweden it is customary to preserve the graft (94).

1.9.2.3 Antibiotic prophylaxis

To minimise the risk of postoperative infection, it is routine to use perioperative antibiotics in almost all kinds of orthopaedic surgery with implants, including ACLR (95, 96). The spectrum of antibiotic resistance differs between countries and, as a result, the choice of antibiotic prophylaxis differs accordingly (97, 98). In Sweden, the drug of choice is cloxacillin, with the alternative of clindamycin in the event of PC allergy (21).

1.9.2.4 Prolonged antibiotic prophylaxis

When the duration of the antibiotic prophylaxis is extended beyond 24 hours, it can be defined as prolonged antibiotic prophylaxis. However, there is no scientific support for using antibiotic prophylaxis for more than 24 hours (98, 99).

1.10 OUTCOME AFTER ACLR

Following ACLR, it is customary to analyse the subjective outcome by using PROMs. Factors associated with superior patient-reported outcomes following ACLR are age less than 18 (100), age of 40 years and older (101), male sex (102), not smoking (103, 104), receiving a hamstring tendon autograft (105) and having no concomitant injuries (106).

Another option is to study the risk of revision ACLR, which has been shown to have an overall risk ranging from 2.1% to 7.7% in studies based on cohorts from 980 to 18,425 patients (107, 108).

1.10.1 Subjective outcome after ACLR complicated by VTE

The patient-reported outcome after ACLR complicated by VTE has, previously, not been reported in the literature. The subjective outcome reported by patients who have undergone surgery for acute Achilles tendon rupture complicated by DVT is significantly lower as compared with those of patients without a DVT. However, the incidence of DVT after surgery for acute Achilles tendon rupture is considerably higher than the incidence of VTE after ACLR, and the populations are not comparable (109).

1.10.2 Subjective outcome after ACLR complicated by SA

The patient-reported outcome following ACLR complicated by SA has been reported in smaller series. In a review by Makhni, including 160 patients with infection and data on the Lysholm score*, no difference was shown between the infected group and the group without infection. In a sub-analysis comprising only 50 patients with infection and data on the International Knee Documentation Committee (IKDC)*, the infected group had significantly lower scores than the group without infection (110).

1.10.3 Risk of revision after primary ACLR complicated by SA

No studies have previously reported the risk of revision ACLR for patients who have undergone a primary ACLR and had a postoperative SA.

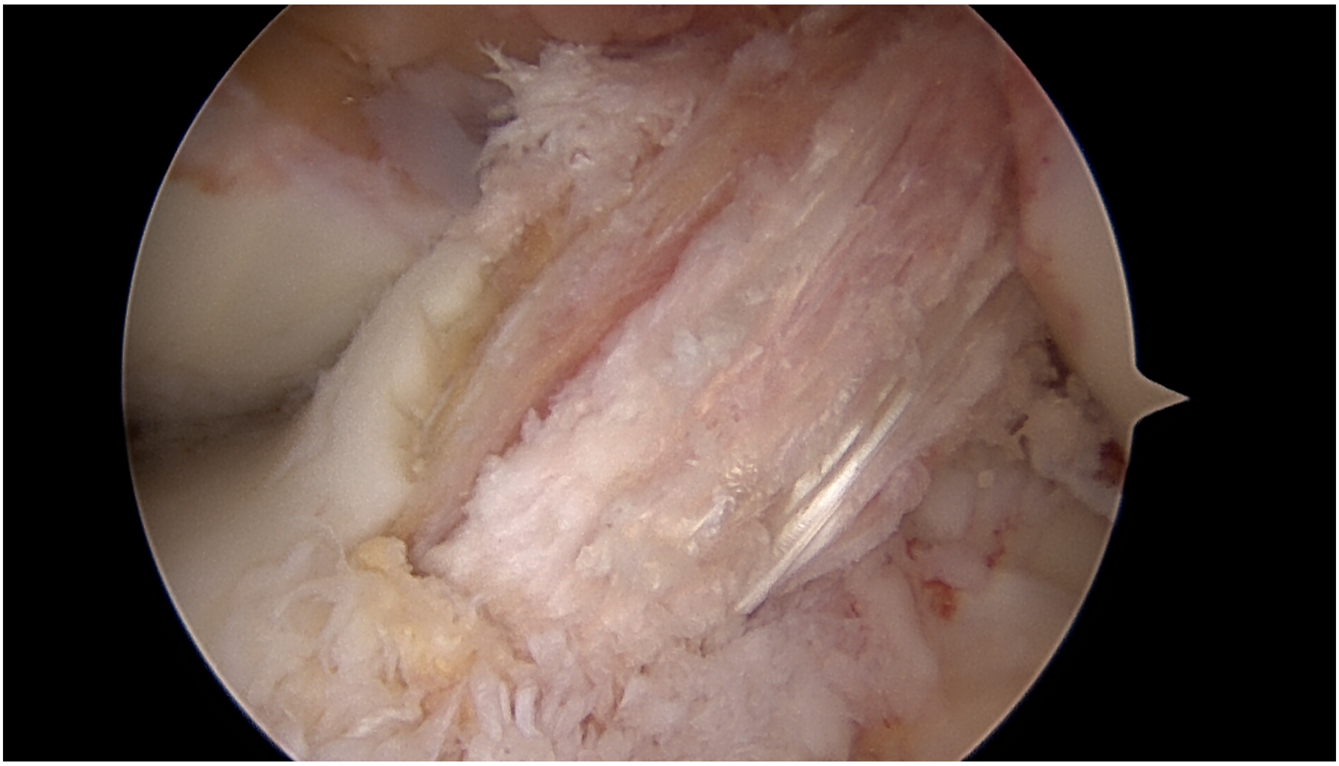

Figure 4c. Same patients as in figure 4b, now with a reconstructed ACL, with graft from the quadriceps tendon.

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* The Lysholm score and IKDC are examples of PROMs that include grading from an observer, which could introduce observer bias.

2 RESEARCH AIMS

The overall aim of this thesis was to describe the incidence of complications after ACLR, its risk factors and the impact on outcome. The specific objectives were:

- To investigate the incidence of VTE and SA after ACLR
- To investigate the risk factors for VTE and SA after ACLR
- To analyse wheter non-respondents at the two-year follow-up in the SKLR differ from respondents, with respect to the baseline and outcome variables, and to analyse reasons for not responding
- To describe the subjective outcome in patients who had a VTE
- To describe the subjective outcome in patients who had SA after a primary ACLR
- To describe the risk of revision ACLR in patients with SA after a primary ACLR

3 MATERIALS AND METHODS

In all four studies, the study populations have been retrieved from the SKLR.

3.1 ANALYSIS OF INCIDENCE AND RISK FACTORS

All primary and revision ACLRs from 2006 to 2013 were defined as the study population in the analysis of incidence and risk factors for VTE and SA, Studies II and III. The cohort was cross-matched with the registers at the National Board of Health and Welfare; the National Patient Register, the Causes of Death Register and the Swedish Prescribed Drugs Register using PINs. Data from the day of surgery until 90 days postoperatively were included.

3.1.1 Venous thromboembolism

VTE was defined by a combination of ICD codes in the NPR and information on the prescription of anti-coagulants ≥ 30 days in the SPDR (Tables 7 and 14, appendix). By combining the two registers, only thromboses which received treatment were included in the analysis. The time to VTE was calculated from the day of surgery to the first registration in the

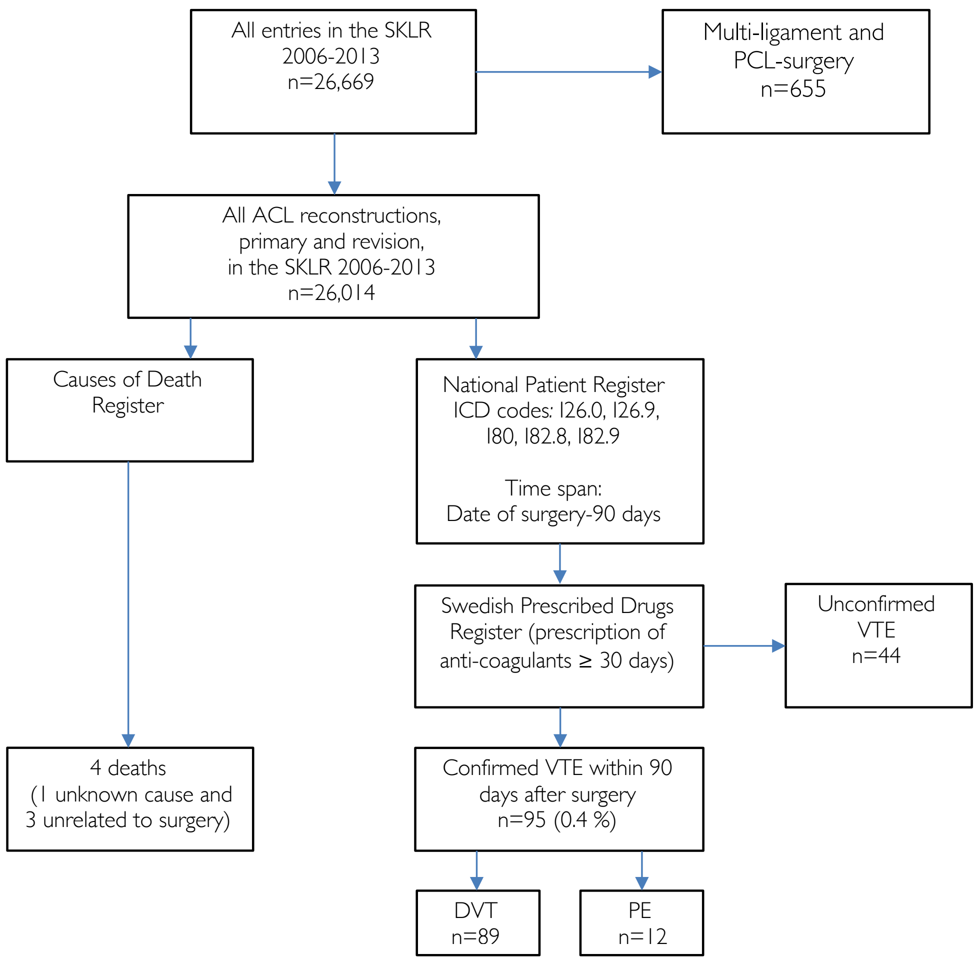

Figure 7. Flowchart of the patient selection in the analysis of VTE after ACLR, Study II.

NPR, with an ICD code indicating VTE. Some patients had a diagnosis of both DVT and PE, which was defined as one event of VTE. The retrieved cohort with patients who had sustained a VTE was compared with patients not having a VTE. The variables included in the analyses were based on information from the SKLR and consisted of sex, smoking, age at surgery, BMI, primary/revision surgery, meniscal repair, in-/out-patient surgery, operating time, choice of graft and the use of thromboprophylaxis. The variable of thromboprophylaxis was retrieved from the SKLR, as some healthcare providers hand out the drug directly to the patient and do not prescribe the drug (Figure 7).

3.1.2 Septic arthritis

The definition of SA was based on a combination of data from the NPR and SPDR. In the NPR, data were retrieved by using the ICD codes M00 and T84 (Table 7, appendix). In the SPDR, data were collected based on the prescription of antibiotics with an appropriate drug, dose and length of prescription for at least two weeks (Table 8, appendix). By combining data from these two sources, the specificity of the study was increased and only included patients who had been prescribed antibiotics. The selection of patients with SA was further enhanced by a national medical record review.

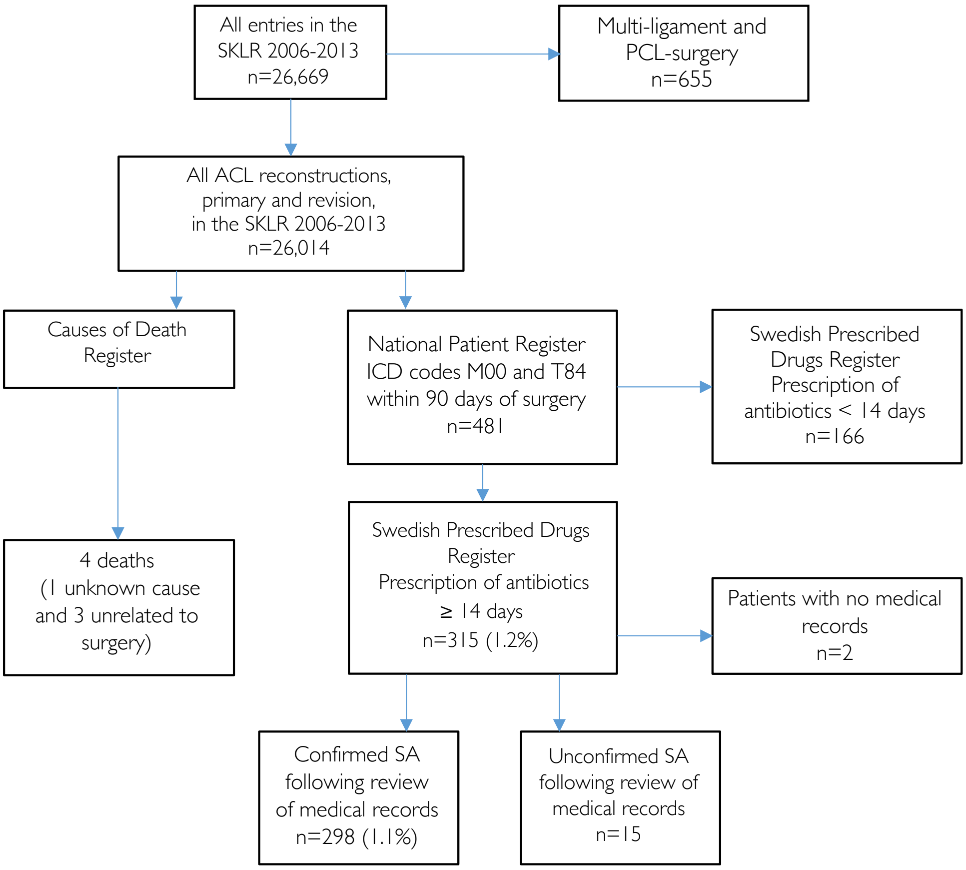

Figure 8. Flowchart of the patient selection in the analysis of incidence and risk factors for SA after ACLR, Study III.

The collection of medical record data included culture findings from joint aspirate and/or biopsy specimens, clinical signs of septic arthritis: fever ≥ 38°C, knee effusion, CRP > 40, analysis of joint fluid with low glucose and increased leukocytes and documented treatment of SA. All patients with a positive culture were included, patients without a positive culture were included if clinical signs of SA were evident. Patients without medical record information were excluded. The time to SA was calculated from the time of surgery until the first registration in the NPR, with an ICD code indicating SA (Figure 8).

The identified cohort with patients who had postoperative SA was compared with patients without SA. Variables retrieved from the SKLR were sex, age at surgery, BMI, smoking, in-/out-patient surgery, primary/revision surgery, cartilage lesion, meniscal suture, choice of graft (hamstring tendon autograft, patellar tendon autograft, allograft and other type of graft), operating time and perioperative antibiotics. Patients who underwent surgery with an allograft and some other type of graft were excluded from the risk factor analysis, since these two categories consisted of small numbers. The variable of perioperative antibiotics was divided into four categories (cloxacillin, clindamycin, cefuroxime and other drugs), with the inclusion of the two most used categories in the risk factor analysis. Diabetes mellitus was defined by using data from the SPDR and, more specifically, information on multiple prescriptions of anti-diabetic drugs. Information on patients with a VTE was retrieved from Study II. Patients who were given a prescription for antibiotics on day 0-2 were defined as having prolonged antibiotic prophylaxis.

3.2 ANALYSIS OF OUTCOME

3.2.1 Analysis of non-response

All patients who had undergone primary or revision ACLR in 2010 were included in the non-response analysis in Study I. The cohort was divided into the two groups, respondents and non-respondents, based on whether the patient had registered or not registered the two-year follow-up questionnaire which consists of the KOOS and EQ-5D. The following variables were extracted from the SKLR: sex, age at surgery, time between injury and surgery, meniscal and/or cartilage lesion, choice of graft, primary or revision surgery and activity at the time of injury.

The non-respondents were sent a reminder via mail with the same two-year follow-up questionnaire, together with a non-response survey. The non-response survey was created after a dialogue with the steering committee of the SKLR. It consisted of two pages, where the first page included information about the study and the second page had two "yes or no" questions (B1 and B2) and five statements (B3-B7) where the patient filled in the level of agreement on a 10-point Likert scale, with 10 representing full agreement. The survey included a box for optional comments (Figure 12).

The change in the KOOS and EQ-5D from preoperatively to two years postoperatively was analysed in the group of respondents and the group of late respondents. Patients who lacked the registration preoperatively were excluded.

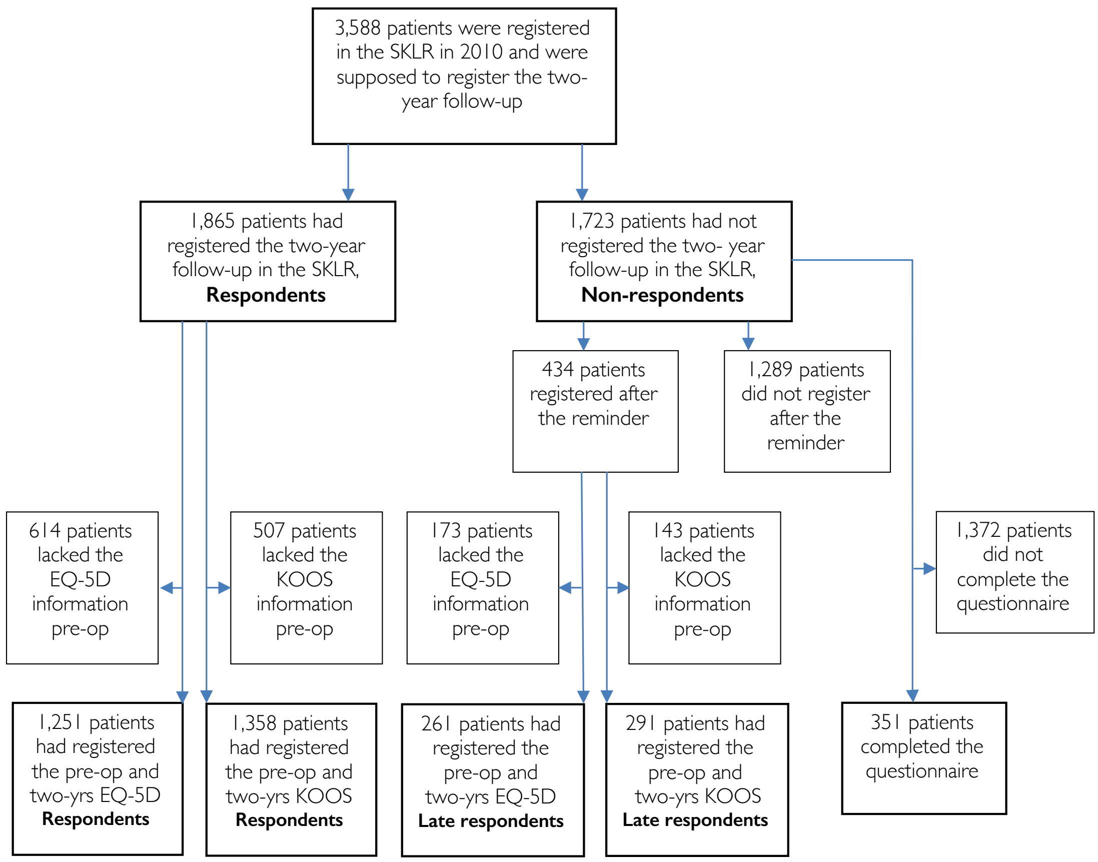

Figure 9. Flowchart of the patient selection in the non-response analysis, Study I.

The number of patients who replied to the KOOS and EQ-5D questionnaires was not consistent with the number of patients who replied to the non-response survey and, as a result, the group in the outcome analysis differs from the group in the non-response survey (Figure 9).

3.2.2 Subjective outcome after venous thromboembolism

The subjective outcome for patients with a postoperative VTE was analysed with the five subscales of the KOOS and the two subscales of the EQ-5D. Patients with VTE were compared with patients with no VTE preoperatively and at one and two years postoperatively.

3.2.3 Outcome after septic arthritis

To study the outcome after ACLR complicated by SA in Study IV, a subgroup of the study population in Study III was used. Patients with a primary ACLR with a hamstring or patellar tendon autograft, registered in the SKLR from 2006 to 2013, were included. ACLRs performed with other types of graft were excluded (Figure 10).

The patients with SA after a primary ACLR were then cross-matched with the SKLR to extract information on subjective outcome data (KOOS and EQ-5D index) during a five-year follow-up. Data on revision surgery were extracted during a five-year follow-up.

Differences between the group of patients with SA and patients without SA were analysed with the following variables from the SKLR: sex, age at surgery, BMI, smoking, in-/out-patient surgery, cartilage lesion, meniscal resection, meniscal suture, operating time, choice of graft and perioperative antibiotics.

The KOOS with five subscales and the EQ-5D index were analysed preoperatively and at one, two and five years postoperatively. Patients who underwent revision surgery during the five-year follow-up had their PROM data included until the event of revision surgery.

The risk of revision ACLR within five years of the primary operation was calculated in the group of patients with SA and compared with patients with no SA.

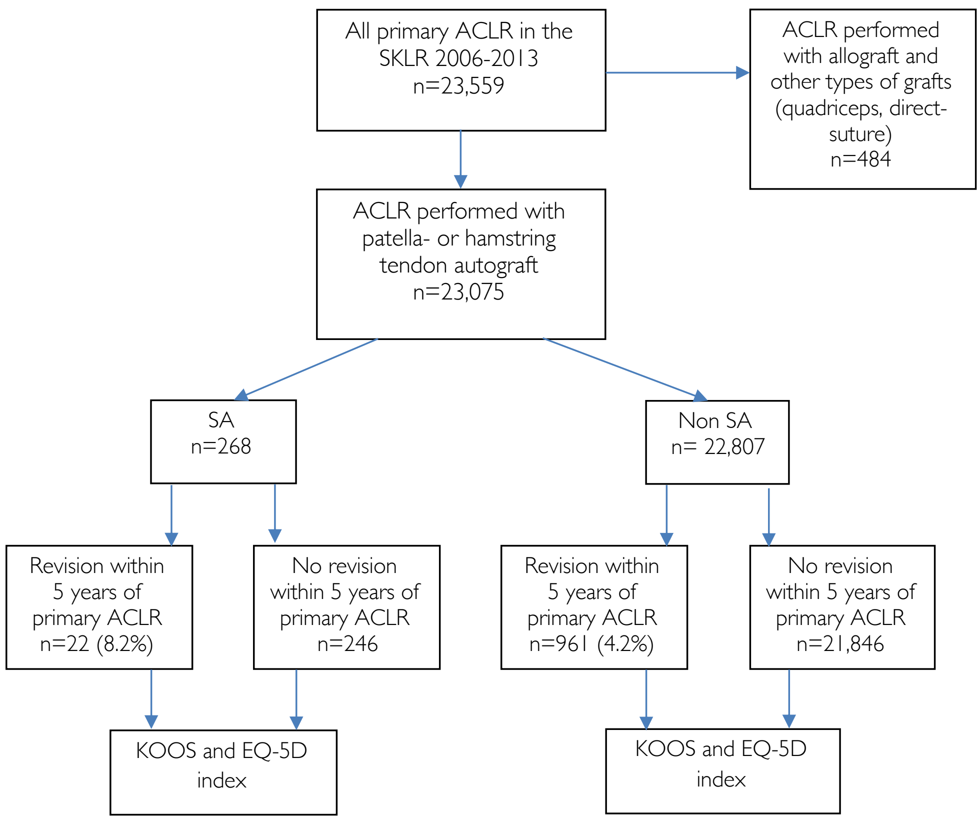

Figure 10. Flowchart of the patient selection in the analysis of outcome after SA, Study IV.

3.3 STATISTICS

Variables have been summarised with standard descriptive statistics such as frequency, mean, median, standard deviation (SD) and range depending on type and distribution of data. Differences between groups of categorical variables, for example, male or female, SA or no SA, were analysed using Pearson's chi-square test. If an expected frequency in any cell was five or less, Fisher's exact test was used. Differences between two groups with continuous variables, for example, mean age at surgery and operating time, were analysed with Student's t-test. In the case of severely skewed variables, non-parametric tests were used, e.g. the Mann-Whitney U test for comparison between independent groups or Kendall's rank correlation coefficient. The level of significance was five per cent (two-tailed) in all analyses.

3.3.1 Analysis of incidence and risk factors

3.3.1.1 Venous thromboembolism

Based on previous knowledge the following variables were assumed to be associated with an increased risk of VTE: sex, age greater or equal to 40 years, thromboprophylaxis, out-patient surgery, revision surgery, meniscal repair and operating time greater than or equal to 90 minutes, and were included in a logistic regression analysis, with results presented as odds ratios (OR) with a 95% confidence interval (CI)(69, 70, 73).

3.3.1.2 Septic arthritis

The baseline analysis presented the following variables with a significant difference: sex, cartilage lesion, operating time, choice of graft and type of perioperative antibiotics. These five variables were included in a logistic regression analysis. Another two variables, BMI and VTE, were significant in the baseline analysis but were excluded from the analysis. BMI was excluded since the variable had a large number of missing values and VTE was excluded due to uncertainty of causality. To include the continuous variable of operating time in the regression analysis, dichotomisation was performed with the unbiased median value of 70.0 minutes as a cut-off. The results of the logistic regression analysis were presented as OR with a 95% CI.

3.3.2 Analysis of outcome

3.3.2.1 Analysis of non-response

In the analysis of non-response, the baseline data for respondents vs non-respondents showed significant differences in sex and age at surgery. The following analyses of group differences were thus made with sex and age at surgery as covariates in an analysis of covariance.

3.3.2.2 Subjective outcome after venous thromboembolism

In the analysis of PROM, age was entered as a covariate, since there was a significant difference in age at surgery between the group with VTE and the group without VTE. The PROMs were analysed separately on each occasion; preoperatively and at one and two years postoperatively. It would have been preferable to use a repeated measurement design, but this would have introduced a great loss of power, since the PROM database in the SKLR is not complete. To exemplify this, in the KOOS variable of Symptoms, only 19 of 95 patients (20%) would have been included, which would have affected the inclusion of all other variables.

3.3.2.3 Outcome after septic arthritis

The KOOS and EQ-5D index were analysed using linear mixed models with the restricted maximum likelihood method to estimate the change over time. Patients were included in the models if they had at least one input of a PROM. The within-subject variable of time was entered as a repeated effect with an unstructured covariance structure. Time and the between-subject variable group and the interaction between time*group were entered as fixed effects in the model. The final models also included the covariates of age at surgery, sex, choice of graft and cartilage injury.

Within-subject effects were presented at each time point with 95% CI and p-value. The between-subjects effect and mean change were presented at each time point with 95% CI and p-value.

Proportional Cox regression was used to calculate the risk of revision ACLR within five years of the primary ACLR. Revision was entered as the status variable, years to revision as the time variable and SA as the prognostic factor in the model. The final models also included the covariates of age at surgery, sex, choice of graft and cartilage injury. Individuals were right censored if they survived up to five years, i.e. no report of an event within the study period, or if they died before the end of the study. The proportional hazard assumption was checked graphically and statistically using a log-minus-log plot entering the group variable of septic arthritis as stratum and by modelling the time*group interaction in a time-dependent Cox model. Non-parallel lines in the log-minus-log plot and a significant interaction effect in the model indicating a time-dependent covariate, i.e. the proportional hazard assumption, was violated.

The hazard ratio (HR) with 95% CI is presented.

3.3.3 Software

All statistical analyses were performed using IBM SPSS Statistics software (versions 25 and 26) for Windows.

3.4 ETHICAL CONSIDERATIONS

Ethical considerations are an important part of any research. The results are presented at a group level and the risk of identifying a specific individual is minimal. All four studies are register based; it is thus relevant to consider the legislation for each register.

3.4.1 The Swedish Knee Ligament Register

The SKLR is regulated by the Patient Data Act and the General Data Protection Regulation (GDPR), previously the Personal Information Act. Once the information is extracted and used for research purposes, the data are regulated by the GDPR. When a patient enters the register, he or she is given the opportunity to opt out.

3.4.2 Registers at the National Board of Health and Welfare

This thesis uses three registers from the National Board of Health and Welfare (NPR, SPDR and CDR), all of which have absolute secrecy. The registers are regulated by the Public Access to Information and Secrecy Act which states, for example, when the secrecy can be voided. There is no consent for these registers and registration is mandatory following a political decision.

3.4.3 Ethical permits

To conduct research on humans, human specimens or sensitive personal information, an ethical permit is mandatory. These permits are processed by the Swedish Ethical Review Authority, which makes its decision according to the Law on Ethical Vetting and the GDPR, among others.

This thesis has three permits from the regional ethics committee in Stockholm (which was replaced by the Swedish Ethical Review Authority on 1 January, 2019): 2011/337-31/3, 2013/1257-31/3 and 2017/408-32.

Applicable laws – Swedish translations

The General Data Protection Regulation (GDPR), EU 2016/679 – Dataskyddsförordningen

The Patient Data Act – Patientdatalag (PDL)(2008:355)

The Personal Information Act – Personuppgiftslag (PUL)(1998:204)

The Public Access to Information and Secrecy Act – Offentlighets- och sekretesslag (OSL)(2009:400)

The Law on Ethical Vetting – Lag (2003:460) om etikprövning av forskning som avser människor

4 RESULTS

4.1 INCIDENCE AND RISK FACTORS

The study population consisted of 25,197 patients. Eight hundred and seventeen patients had two or more operations and the total number of ACLRs was 26,014, of which 1,619 (6.2%) were revision procedures. Three patients died of unrelated causes such as a gunshot wound, fall from height and alcohol-related death. One patient, a 21-year-old man, died of an unknown cause, 58 days following surgery.

4.1.1 Venous thromboembolism

The total number of VTEs was 95 (0.4%) with a mean time from surgery to VTE of 15.1 days (range 1 to 86)(Figure 7). Differences between the group with VTEs as compared with the group without VTEs are presented in Table 9, appendix. The only independent risk factor for VTE following the logistic regression analysis was age at surgery greater than or equal to 40 years (odds ratio 2.31, 95% CI 1.45-3.70)(Table 1). Thromboprophylaxis was prescribed at 36.4% of the performed surgeries, with no difference between the group with VTE and the group without VTE.

Table 1. Risk factors for venous thromboembolism in a logistic regression analysis

	Reference category	*Beta coefficient*	*Odds ratio*	*95% CI*	*p-value*
Patient demographics					
Male sex	*Female sex*	0.26	1.30	0.85-1.98	0.232
Age ≥40 yrs	*< 40 yrs*	0.84	2.31	1.45-3.70	<0.001
Thromboprophylaxis	*No thromboprophylaxis*	0.11	1.11	0.72-1.71	0.628
Perioperative data					
Out-patient surgery	*In-patient surgery*	0.60	1.83	0.99-3.37	0.053
Revision surgery	*Primary surgery*	0.03	1.03	0.42-2.56	0.946
Meniscal repair	*No meniscal repair*	0.60	1.83	0.91-3.69	0.092
Operating time ≥90 min	*< 90 min*	-0.49	0.62	0.36-1.04	0.072
Constant	*n/a*	-6.99	n/a	n/a	n/a

CI, confidence interval, n/a, not applicable

4.1.2 Septic arthritis

The total number of SA identified in the cohort of 26,014 ACLRs was 298, corresponding to an incidence of 1.1% (Figure 8). The 16 high-volume units, with ≥ 500 ACLRs during the study period, had a distribution of SA from 2 to 47 (0.2-2.9%) and there was no significant difference compared with the distribution in the low-volume units (1.1 vs 1.2%, p=0.273). The mean time from surgery to diagnosis of SA was 18.4 days (range 1 to 74). Differences between the group with SA and the group without SA are presented in Table 13a and 13b, appendix.

The logistic regression analysis of the risk factors established male sex, operating time ≥ 70 minutes, a hamstring tendon autograft and clindamycin as independent risk factors for SA (Table 2).

Table 2. Risk factors for septic arthritis in a logistic regression analysis

	Reference category	Beta coefficient	Odds ratio	95% CI	p-value
Patient demographics					
Male sex	*Female sex*	0.50	1.65	1.28-2.13	<0.001
Perioperative data					
Cartilage lesion	*No cartilage lesion*	0.24	1.27	0.99-1.63	0.062
Operating time ≥ 70 min	*< 70 min*	0.61	1.83	1.42-2.36	<0.001
Hamstring tendon autograft	*Patellar tendon autograft*	0.80	2.23	1.21-4.08	0.010
Clindamycin	*Cloxacillin*	0.66	1.94	1.10-3.41	0.022
Constant	*n/a*	-7.14	n/a	n/a	n/a

CI, confidence interval; n/a, not applicable

4.2 OUTCOME

4.2.1 Analysis of non-response

4.2.1.1 Validation of key baseline data

The study of non-response included 3,588 patients, of which 41.1% were females. At the two-year follow-up, 1,865 were respondents and 1,723 were non-respondents. The respondents had a significantly higher age at surgery and contained a greater proportion of females than the non-respondents (Table 3).

Table 3. Baseline data for respondents and non-respondents.

	Respondents (n=1,865)	Non-respondents (n=1,723)	p-value
Sex			
Female, n=1,476	927 (62.8%)	549 (37.2%)	<0.001
Male, n=2,112	938 (44.4%)	1,174 (55.6%)	
Age, years (range)	27.8 (9-64)	25.9 (12-65)	<0.001
Time to surgery, days (SD)	244 (4.44)	256 (4.84)	0.074

SD, standard deviation

4.2.1.2 Analysis of KOOS and EQ-5D

The KOOS and EQ-5D for respondents and late respondents, preoperatively and at two years postoperatively, are presented in Table 10 and 11, appendix. The improvement in the KOOS from preoperatively to two years postoperatively is displayed in Figure 11, where the subscales of Pain and Knee-Related Quality of Life show significantly lower scores for the late respondents as compared to the respondents. The analysis of the EQ-5D revealed no significant differences between the two groups (Figure 15, appendix).

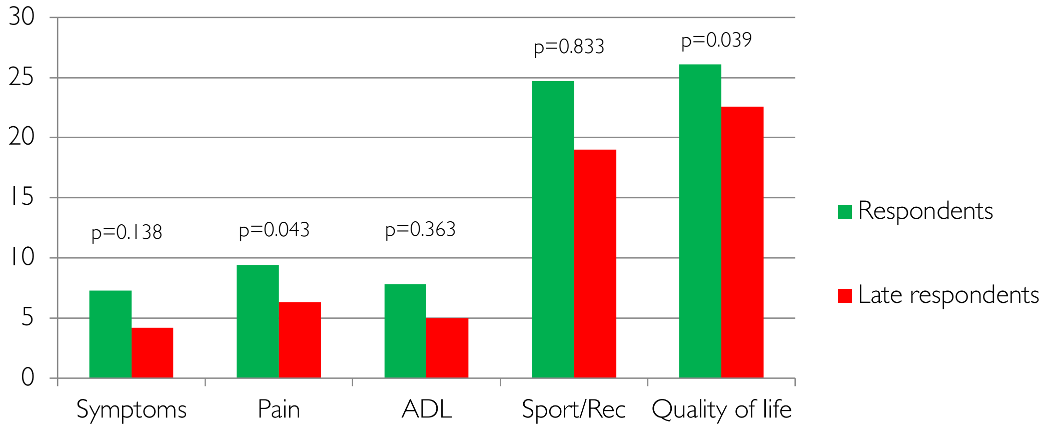

Figure 11. The improvement in the KOOS from preoperatively to the two-year follow-up presented in each subscale for respondents and late respondents. Data adjusted for age at surgery and sex. ADL, activity of daily life; Sport/Rec, sport and recreational function

4.2.1.3 Non-response survey

The non-response survey had a response rate of 20.3%, with 40.3% women. The first question, B1 "Did you, at the time of surgery, receive information about the SKLR", only had a 60% level of agreement. The percentage of agreement of statements B3-B7 was below 32% (Figure 12).

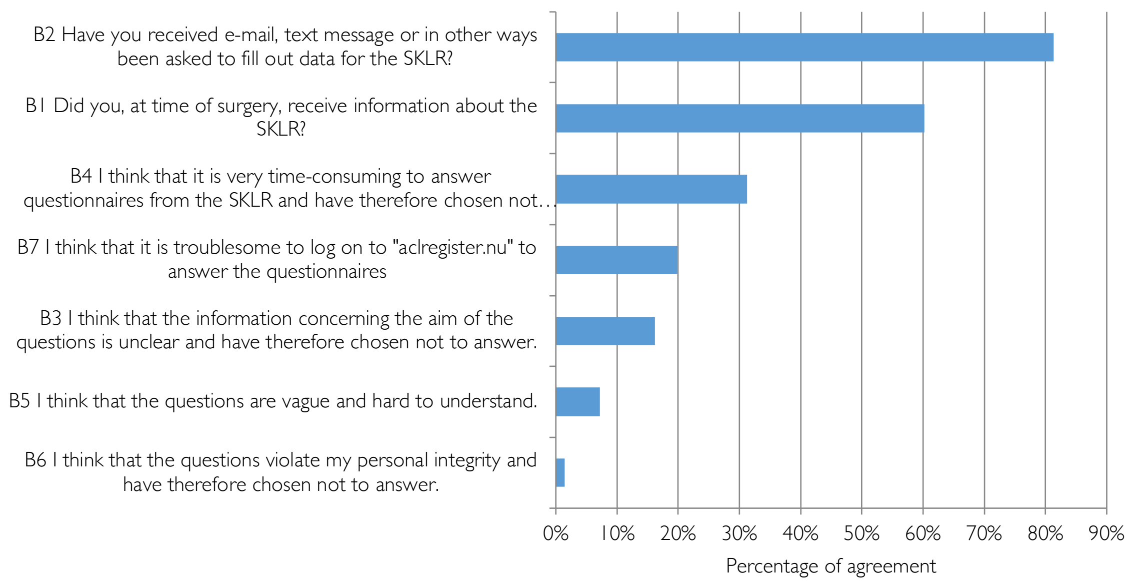

Figure 12. Percentage of agreements with items B1-B7 in the non-response survey.

4.2.2 Subjective outcome after venous thromboembolism

The group with VTE had a significantly poorer outcome on all subscales of the KOOS and EQ-5D compared with the group without VTE at one year postoperatively. At two years postoperatively, the difference remained but was only statistically significant in the KOOS subscales of Activity of daily living (85.9 vs 90.8, p=0.030) and Sport and recreational function (55.3 vs 64.3, p=0.046)(Table 12, appendix).

4.2.3 Outcome after septic arthritis

The outcome after SA was analysed in a subgroup from the incidence analysis and included 23,075 primary ACLRs, with 268 (1.2%) events of SA. The within-subject and the between-subject effects are presented in Table 4. The fixed effects of time*SA were significant in the KOOS subscales of Symptoms, Pain, Sport and recreational function and Knee-related quality of life (Figure 14).

The overall rate of revision ACLR was 4.3%. Patients with SA ran an increased risk of revision ACLR, with an adjusted HR of 2.04 (95% CI 1.34 to 3.12)(Figure 13). The median time to revision surgery was 800 (range from 254 to 1,825) days for patients with SA and 1,020 (range from 42-1,825) days for patients without SA.

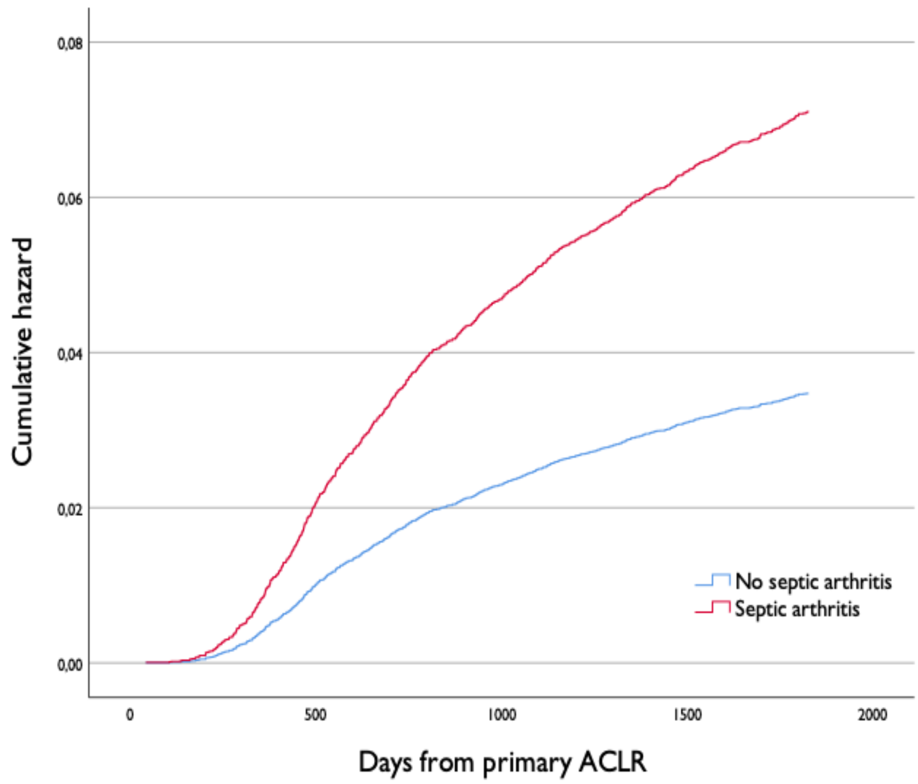

Figure 13. Adjusted, cumulative hazard rate for revision ACLR, within five years of primary surgery.

Table 4. Mean scores of the KOOS subscales and the EQ-5D index for patients with and without septic arthritis. Scores are presented preoperatively and at one, two and five years postoperatively, with within-subjects and between-subjects effects. Data is adjusted for age at surgery, sex, cartilage lesion and choice of graft.

		Within-subjects effects										Between-subjects effects				
		No septic arthritis					Septic arthritis					At each time-point	Change at each time point			
	Year	n	Mean score	95% CI Lower	95% CI Upper	p-value	n	Mean score	95% CI Lower	95% CI Upper	p-value	p-value	Mean score	95% CI Lower	95% CI Upper	p-value
KOOS Symptoms	Preop	15,819	69,5	69,2	69,8	-	184	67,4	64,8	70,0	-	0.120	-	-	-	-
	1	13,893	76,7	76,4	77,0	<0.001	149	70,5	67,8	73,2	0.059	<0.001	4.1	0.8	7.3	0.014
	2	11,986	77,4	77,1	77,7	<0.001	133	70,2	67,4	73,0	0.100	<0.001	5.1	1.8	8.5	0.003
	5	10,336	79,4	79,0	79,7	<0.001	106	70,4	67,3	73,5	0.106	<0.001	6.9	3.2	10.5	<0.001
KOOS Pain	Preop	15,819	74.1	73.8	74.4	-	184	72.6	70.1	75.1	-	0.259	-	-	-	-
	1	13,892	84.1	83.9	84.4	<0.001	149	79.3	76.9	81.6	<0.001	<0.001	3.4	0.6	6.2	0.019
	2	11,988	83.8	83.6	84.1	<0.001	133	78.7	76.2	81.2	<0.001	<0.001	3.7	0.6	6.7	0.018
	5	10,332	85.1	84.8	85.4	<0.001	106	78.2	75.4	81.0	0.001	<0.001	5.5	2.1	8.8	0.001
KOOS ADL	Preop	15,818	83.2	83.0	83.5	-	184	80.0	77.6	82.5	-	0.010	-	-	-	-
	1	13,893	91.1	90.9	91.3	<0.001	149	86.2	84.2	88.1	<0.001	<0.001	1.8	-0.8	4.3	0.177
	2	11,987	90.6	90.4	90.8	<0.001	133	86.0	83.8	88.1	<0.001	<0.001	1.5	-1.3	4.2	0.294
	5	10,335	91.0	90.8	91.3	<0.001	106	85.4	83.0	87.7	<0.001	<0.001	2.5	-0.4	5.4	0.096
KOOS Sport/Rec	Preop	15,820	40.0	39.6	40.4	-	184	38.6	34.8	42.4	-	0.479	-	-	-	-
	1	13,891	64.0	63.5	64.4	<0.001	149	54.0	49.9	58.0	<0.001	<0.001	8.6	3.8	13.4	<0.001
	2	11,985	64.5	64.0	64.9	<0.001	133	53.6	49.3	57.9	<0.001	<0.001	9.5	4.4	14.6	<0.001
	5	10,331	66.0	65.5	66.5	<0.001	106	54.6	49.7	59.5	<0.001	<0.001	10.1	4.4	15.7	0.001
KOOS QoL	Preop	15,818	33.1	32.8	33.4	-	184	32.7	30.1	35.4	-	0.792	-	-	-	-
	1	13,894	57.9	57.5	58.3	<0.001	149	49.8	46.2	53.4	<0.001	<0.001	7.7	3.7	11.7	<0.001
	2	11,986	59.5	59.1	59.9	<0.001	133	49.9	46.1	53.8	<0.001	<0.001	9.2	4.9	13.4	<0.001
	5	10,335	62.5	62.0	62.9	<0.001	106	51.4	47.0	55.8	<0.001	<0.001	10.8	5.9	15.6	<0.001
EQ-5D index	Preop	14,754	0.68	0.67	0.68	-	165	0.65	0.61	0.68	-	0.018	-	-	-	-
	1	13,910	0.80	0.80	0.80	0.002	151	0.74	0.70	0.77	0.021	0.016	0,036	-0.006	0.077	0.095
	2	11,734	0.80	0.80	0.81	0.002	129	0.74	0.70	0.77	0.022	0.017	0,036	-0.008	0.080	0.109
	5	10,099	0.82	0.82	0.82	0.002	103	0.77	0.73	0.80	0.024	0.019	0,027	-0.020	0.074	0.265

CI, confidence interval; ADL, activity of daily living; Sport/Rec, Sport and recreational function; QoL, Knee-related quality of life.

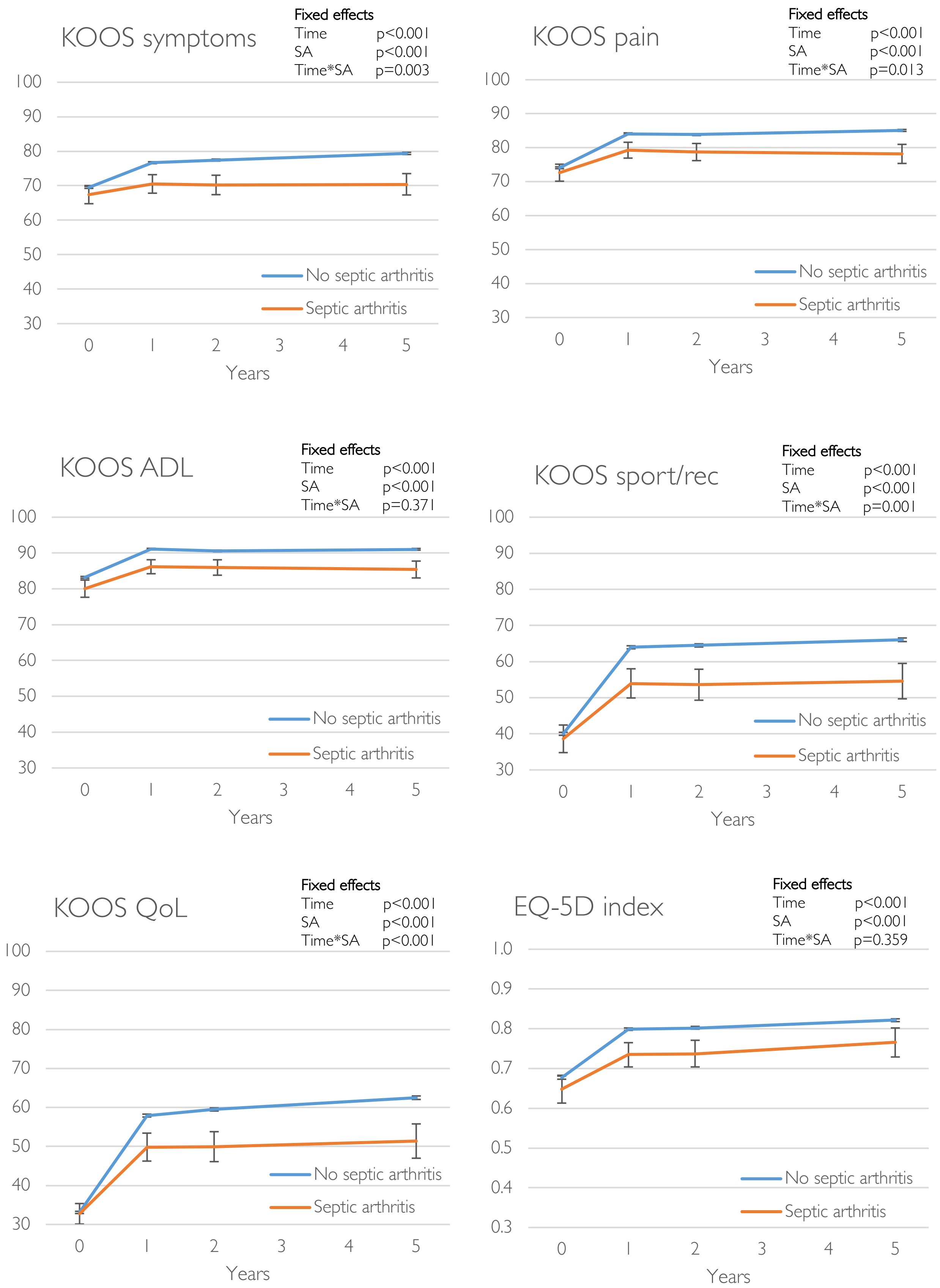

Figure 14. Mean values of the KOOS subscales and the EQ-5D index for the groups with and without septic arthritis, preoperatively (0 years) and at each follow-up occasion (1, 2 and 5 years postoperatively). Adjusted for the covariates age at surgery, sex, cartilage lesion and choice of graft.
Whiskers displaying 95 % confidence interval.
SA, septic arthritis; ADL, activity of daily living; sport/rec, sport and recreational function; QoL, knee-related quality of life

5 DISCUSSION

By combining different types of registers, this thesis presents two rare complications following ACLR. The incidence, the risk factors and the outcome of VTE and SA are investigated and established.

5.1 INCIDENCE AND RISK FACTORS FOR VENOUS THROMBOEMBOLISM

The finding of an incidence of VTE after ACLR of 0.4% is low and in agreement with previous published literature (69, 70, 111). The corresponding incidence in a general population in the age group of 25-35 years is 0.03%, while it is 0.07% in a middle-aged female population (65, 112). However, when calculating the risk of VTE during a three-month period for these two study populations, the risk decreases to 0.008% and 0.018% respectively. Based on these findings, the risk of a VTE within three months of an ACL reconstruction is 20 to 50 times higher as compared with a population not having surgery.

Table 5. Reports on the incidence of and risk factors for VTE after ACLR

Author	*Year published*	*Study population, n*	*Incidence of VTE*	*Identified risk factors*	*Odds ratio, (CI)*
Jameson et al. (69)	2012	13,491	0.4%	Age > 40 years*	2.36 (1.29-4.34)*
Maletis et al. (111)	2013	16,192	0.3%	Not reported	-
Gaskill et al. (70)	2015	16,558	0.5%	Age ≥ 35 years†	1.96 (1.27-3.04)†
				Use of NSAID	0.44 (0.28-0.70)
				Use of anticoagulants	98.32 (61.63-156.86)
Kraus Schmitz et al.	2019	26,014	0.4%	Age ≥ 40 years*	2.31 (1.45-3.70)*

CI, confidence interval, *multivariate analysis, †univariate analysis

Table 5 illustrates previous findings of incidence and risk factors for VTE compared with the results of this thesis. The study populations are somewhat smaller, but the findings are similar, with the exception of the study by Gaskill et al., who report risk factors from a univariate analysis. A higher incidence, between 7% to 14%, is reported when patients are screened postoperatively for VTE; with approximately half being asymptomatic (71, 72, 74). One explanation of the diverging incidence of VTE between studies with postoperative screening and no screening is that the symptoms of VTE are similar to the normal symptoms in the early postoperative period, where the leg is swollen and painful, and difficult to differentiate from each other.

The risk factor of older age is reported in the majority of studies listed in Table 5. Age is a known risk factor for VTE in a general population (65). Specific risk factors in the ACLR setting have not been identified by the register-based studies in Table 5. Operating time of more than 90 minutes has been associated with an increased risk of PE in a study by Hetsroni et al., of 418,323 knee arthroscopic procedures, which also demonstrated that ACLR has a lower, albeit not significant, risk of PE as compared with having a meniscectomy (73). The increased risk of PE with a longer operating time could be attributed to the use of a tourniquet, a variable not included in the study by Hetsroni et al., whereas Dong et al. reported a relative risk of DVT in patients having a tourniquet for > 120 minutes of 3.6 as compared with patients having a tourniquet for < 90 minutes (74). However, the data from Dong et al. included multi-ligament procedures and the risk factor analysis was univariate. The risk of tourniquet use during surgery has not been fully investigated. Hirota et al. analysed the amount of emboli formation in the right atrium with transoesophageal echocardiography following the deflation of a tourniquet. They compared patients who underwent ACLR and total knee arthroplasty (TKA) and found that both groups had a substantial increase in emboli at the time of deflation with significantly more emboli in the group that underwent TKA. They also found that the number of emboli correlated positively to tourniquet time in both groups. Despite the formation of emboli, no PE was detected among the 40 patients (113). In a meta-analysis of patients who underwent TKA with and without the use of a tourniquet, no difference in the occurrence of DVT or PE was demonstrated (114). The SKLR does not include information on the use of a tourniquet, but Ekdahl et al. reported that more than half the Swedish ACL surgeons always use a tourniquet (76).

Female sex was shown to be an independent risk factor for PE in the study by Hetsroni et al. (73). In a general population, no such relationship has been proven (65). The finding by Hetsroni et al. could be explained by the use of oral contraceptives, a known risk factor for VTE (115). The data presented in this thesis did not reveal any difference between female and male patients and no data on oral contraceptives were included.

Thromboprophylaxis was prescribed to approximately one third of the patients in the study of VTE, with no difference between the group with VTE and the group without VTE. There are no specific recommendations for thromboprophylaxis in the ACLR setting and the American College of Chest Physicians only recommends thromboprophylaxis if the patient has a history of thrombosis (75). A Dutch study by van Adrichem of 1,451 patients undergoing knee arthroscopy was unable to prove any benefit of thromboprophylaxis (116). In the study by Gaskill et al., 147 (0.9%) patients received thromboprophylaxis and had an increased risk of VTE. This paradoxical finding is explained by a probable selection bias, i.e. the patients receiving thromboprophylaxis were probably identified as having a high risk of thrombosis. Based on the findings in this thesis, it was therefore inappropriate to draw any conclusions regarding thromboprophylaxis.

5.2 INCIDENCE AND RISK FACTORS FOR SEPTIC ARTHRITIS

The incidence of septic arthritis after ACLR was 1.1%. All types of surgery include a risk of postoperative infection, which has a probable effect on the outcome. In orthopaedic surgery, arthroplasty of the knee and hip are common procedures, and the incidence of periprosthetic joint infection after hip arthroplasty is reported to be around 1% and from 1% to 2% for knee arthroplasty (117).

The incidence of SA in this thesis is compared with previous findings from register-based studies in Table 6. The methods for establishing a postoperative SA differ between the studies. However, none of the studies has used the method applied in this thesis, where several different sources of information (diagnosis codes, prescription of antibiotics and medical records) are combined in order to establish an incidence with a high specificity and a sensitivity. The low loss to follow-up could be one explanation of the higher incidence as compared to the studies by Brophy and Westermann. This is further illustrated by findings from studies at single institutions, which have a low loss to follow-up and report a higher incidence of SA, from 0.6 to 1.8% (87, 88, 94, 118).

Table 6. Reports on the incidence of and risk factors for SA after ACLR

Author	*Year published*	*Study population, n*	*Incidence of SA*	*Identified risk factors*	*Odds ratio, (CI)*
Westermann et al. (85)	2017	6,398	0.3%	Hospital admission	2.67 (1.65-3.69)*
Brophy et al. (90)	2015	2,198	0.8%	Diabetes mellitus	18.8 (3.76-93.97)*
				Graft choice (HT vs PT)	4.63 (1.20-17.91)
Cancienne et al. (86)	2016	13,358	1.0%	Tobacco use	2.3 (1.6-3.4)†
Kraus Schmitz et al.	2021	26,014	1.1%	Male sex	1.65 (1.28-2.13)*
				Operating time ≥ 70 min	1.83 (1.42-2.36)
				Graft choice (HT vs PT)	2.23 (1.21-4.08)
				Choice of antibiotics (CL vs CX)	1.94 (1.10-3.41)

CI, confidence interval; HT, hamstring tendon autograft; PT, patellar tendon autograft; CL, clindamycin; CX, cloxacillin; *multivariate analysis, †univariate analysis

Another explanation for the somewhat diverging incidence of SA is the choice of graft, which has been proposed to have an impact on the incidence of SA. In this thesis, the majority of the ACLRs, 91%, were performed with hamstring tendon autografts. Previously, the hamstring tendon autograft as compared to the patellar tendon autograft has been reported as a risk factor for SA after ACLR (90, 119, 120), a finding confirmed by this thesis, where hamstring tendon autograft is an independent risk factor for postoperative SA after ACLR as compared to the use of a patellar tendon autograft, with more than double the odds of sustaining a postoperative SA. It is postulated that the hamstring tendon is more easily contaminated during harvest and preparation, before insertion into the knee joint (90, 119, 120). This is further supported by a study on soaking the graft in vancomycin, where seven of 50 grafts were contaminated during harvest or preparation but had negative cultures following soaking the graft with vancomycin (121). Another aspect and possible cause of the increased risk of infection is that the hamstring tendon is normally folded twice (quadrupled) and has a larger surface exposed to bacteria as compared to patellar tendon autografts and quadriceps tendon autografts, which are prepared "en bloc". During the study period of this thesis, vancomycin was not used to soak the graft during preparation. In a survey of Swedish ACL surgeons in 2017, 8% reported the use of vancomycin to soak the graft (76).

Perioperative antibiotic prophylaxis was used in all ACLRs and the use of clindamycin instead of cloxacillin increased the risk of SA with an, almost, doubled odds ratio. This is a novel finding in the ACLR setting. In a report from the Swedish Knee Arthroplasty Register, the risk of revision surgery due to infection was doubled when clindamycin was used instead of cloxacillin as the perioperative antibiotic (122). In Sweden, the use of clindamycin is reserved for patients reporting an allergy to penicillin. However, Robertson et al. emphasised that, with a more detailed history of the patient's report of allergy, a possible type I allergy can be ruled out and a second- or third-generation cephalosporin can safely be used. The reason for the inferior effect of clindamycin has not been established. Robertson et al. point out two possible reasons; its bacteriostatic mechanism compared with beta-lactams, which have a bacteriolytic effect, and the dilution of the drug due to a high intracellular distribution (122).

Prolonged antibiotic prophylaxis, i.e. when the patient is prescribed oral antibiotics for a number of consecutive days following surgery, was used in 6.5% of all ACLRs, with no statistical difference between the group with SA and the group without SA. There is no scientific support for using prolonged prophylaxis and it is thought that its use could increase antibiotic resistance (98, 99).

This thesis showed that an operating time of more than or equal to 70 minutes as compared to less than 70 minutes increased the risk of infection with an OR of 1.83. The relationship between longer operating times and the risk of infection has previously been established in surgical procedures in general (123), as well as in the ACLR setting (124). The mechanism by which the risk of infection is increased is not fully established. In open surgery, the wound has a longer exposure to the environment and potential bacterial contamination (123), but this is not fully applicable in ACLR, where most of the surgery is performed through two or three portals with openings of less than two centimetres and a small, approximately 3-5 cm incision for graft harvesting. However, the instruments are taken in and out of the portals, which is a probable source of contamination, as well as the graft contamination mentioned previously. With longer operating times, there is a risk of fatigue in the surgical team, which could increase the risk of surgical errors (123).

Male sex was another independent risk factor for SA after ACLR, with an OR of 1.65, which is lower than the other presented risk factors. This is a novel finding in ACL surgery, but it has been demonstrated in total knee arthroplasty surgery (125, 126). In SA following invasive pneumococcal disease, male sex has been shown to be an independent risk factor (127). With the data presented in this thesis, the risk factor of male sex cannot be explained.

5.3 OUTCOME

Knowledge regarding the outcome of the two rare complications, VTE and SA, facilitates the decision on how and when preventive measures should be used. The possible lethal outcome of VTE is discussed earlier in the background section. This thesis clarifies the subjective knee function of patients who experienced the complications of VTE and SA, as well as the risk of revision ACLR after SA.

5.3.1 Non-response analysis

With increasing follow-up times, the response rates to the KOOS and EQ-5D questionnaires decreases in the SKLR. The non-response analysis demonstrated small differences of KOOS between the response and non-response groups with questionable clinical outcome.

Women and older patients responded to a greater degree than men and younger patients, which is in agreement with previous study findings (128-130). This is important knowledge, since it has previously been shown that sex and age influence the KOOS. Female patients respond with a poorer KOOS as compared to male patients in several studies (102, 131, 132) and no difference in objective knee function between the sexes has been established (131, 132). The patient's age appears to influence the reported subjective outcome, but the results from previous studies diverge. Desai et al. report that patients aged 40 years and older have a lower preoperative KOOS and a greater improvement in the KOOS compared with younger patients (101), which could suggest that the older patients that undergo surgery have a poorer function and have more to gain from surgery. In contrast, several authors report a higher postoperative KOOS in younger patients (100, 133).

The non-response analysis of the KOOS showed that, after adjustment for age and sex, there was a significantly greater improvement, from preoperatively to the two-year follow-up in the subscales of Pain and Knee-related Quality of Life, for the respondents compared with the late respondents. Whether or not these differences are clinically applicable remains to be answered, but this should at least be considered when analysing the subjective outcome data.

The reasons for not responding were investigated with a separate questionnaire which had a response rate of 20%. Among the respondents to the questionnaire, 40% answered that they had not been given information about the SKLR preoperatively, which indicates that there is room for improvement regarding information about the SKLR given to the patient.

5.3.2 Subjective outcome after venous thromboembolism

The KOOS and EQ-5D were analysed at the one- and two-year follow-ups for patients with VTE and compared with patients without VTE. The former group had poorer outcomes on all follow-up occasions at one year and in the KOOS subscales of Activity of daily life and Sport and recreational function at two years. This is a novel finding with subjective outcome data for patients with a VTE following ACLR and one possible explanation of the initially poorer outcome could be a delay in rehabilitation due to the VTE.

5.3.3 Outcome after septic arthritis

The outcome for patients with SA after primary ACLR was analysed with the KOOS and EQ-5D index preoperatively and at one, two and five years postoperatively and with the five-year risk of revision ACLR.

On all the postoperative follow-up occasions, patients with SA presented with a significantly poorer outcome compared with patients without SA. The patients without SA experience a gradual improvement in the KOOS on each follow-up occasion. The opposite is seen among patients with SA in the KOOS subscales of Symptoms, Pain, Sport and recreational function and Knee-related quality of life, where the scores are without change or even worse at the two- and five-year follow-ups compared with the one-year follow-up. The same subscales demonstrate a significant improvement with time for the group without SA compared with the group with SA. Overall, this analysis demonstrates that patients with SA after primary ACLR have a poorer long-term subjective outcome.

The subjective outcome after ACLR complicated by SA is reported in several studies but with a small number of patients with SA and with different types of outcome scores. Makhni et al.

presented a review with data on the Lysholm score, with no difference between 160 infected patients and patients without infection, and data on the IKDC score, where the infected patients obtained lower scores than patients without infection (110). However, the data presented in the review only included the infected patients and data on the control groups were taken from other studies of uninfected patients.

Boström Windhamre et al. presented data from a Swedish clinic on 27 patients with a postoperative SA. During a follow-up of 60 months, no difference in the improvement of the KOOS could be noted between patients with and without SA (94). Similar findings, with no difference between the groups, were presented by Abdel-Aziz et al. for 24 patients with a postoperative SA during a follow-up period of 59 months (134).

The explanation for the lower PROMs among patients with SA has not yet been established. The pathogenesis in septic arthritis is complex and depends on numerous factors such as the host immune response and the pathogen. The joint damage can be divided into three mechanisms; the bacterial toxins and enzymes, which have a direct injurious effect on the cartilage, the host inflammation response, with the release of collagen-degrading enzymes, and asphyxia in the joint, due to an increase in intra-cellular pressure (78, 81). In a Norwegian study, Rötterud et al. demonstrated that patients with a focal full-thickness cartilage lesion at the time of ACLR had a poorer outcome and a poorer improvement in the KOOS compared with patients without cartilage lesions (135). Based on these findings, it is possible that the lower PROM among the patients with SA is explained by the cartilage deterioration caused by the infection and a more rapid development of osteoarthritis (136, 137). Other explanations include the risk of developing arthrofibrosis following an infection, which affects the outcome negatively (138).

Revision ACLR within five years of primary ACLR was almost twice as high in the group with SA (8.2%) compared with the group without SA (4.2%), which is a novel finding in the ACLR setting. Following an adjustment for previously identified risk factors for revision surgery, age at surgery, sex, graft choice and cartilage lesions, the hazard ratio for patients with SA indicated more than twice the risk of revision ACLR. This finding, together with the finding of a poorer subjective outcome, could indicate that the graft is of poorer quality and runs an increased risk of failure, among patients with SA after primary ACLR.

6 STRENGTHS AND LIMITATIONS

The main strengths of this thesis are the presentation of novel findings from the risk factor analyses and the finding of poorer outcome for patients with a postoperative SA after ACLR. These findings are important to recognise in order to improve the care of patients who undergo ACLR, both to decrease the risk of complications but also to better support the patients which, after all is affected. Using a nationwide population of considerable size and methods for combining registers and review of medical records, it is probable that the incidence and risk factor analyses have yielded high sensitivity and specificity.

However, the use of registers has limitations. To establish the true incidence of the complications and the impact on outcome, a follow-up of 100% is needed and, to evaluate the risk factors accurately, a cohort that is of considerable size is desirable. The combination of these two aspects is difficult to achieve. An analysis of registers is normally associated with a loss to follow-up, whereas the number of included patients can be extensive. The opposite is normally applied to a prospective study at a single institution, where a follow-up of 100% is achievable, but the study population is normally smaller.

As mentioned in the literature review section, two important factors in a register are coverage and completeness. The SKLR is estimated to have completeness of more than 90%, which could introduce a selection bias, as we have no information on the patients who underwent surgery and were not registered in the SKLR (21).

The registers at the Swedish National Board of Health and Welfare are modelled to have coverage of 100%. The completeness is dependent on various circumstances, e.g. the NPR is dependent on the coding made by the treating doctor, whereas the registration in the SPDR is automated with the transfer of data from the Swedish eHealth Agency to the Swedish National Board of Health and Welfare on a monthly basis (54-56). Another aspect is the correctness of the register and the in-patient register (a part of the NPR) has an overall positive predictive value (PPV) of 85-95% (53).

6.1 SPECIFIC LIMITATIONS REGARDING THE ANALYSIS OF INCIDENCE

6.1.1 Venous thromboembolism

Different degrees of uncertainty are attributed to the diagnosis codes for DVT and PE. Öhman et al. presented data from the NPR and CDR from 1985 to 2014 and found a PPV of 81% for PE and 59% for DVT. They concluded that the data on DVT should not be used without validation (139). Alotabi used a Canadian database to demonstrate PPVs of 71% and 77% for PE and DVT respectively (140). The sensitivity of using diagnosis codes for VTE was 75% (140). In this thesis the SPDR was used to confirm and validate the findings of VTE, a method previously used in the US and on Danish register data (141, 142). Using this method, the PPV increases close to 100%, as false positive cases, i.e. patients who are misdiagnosed as VTE, are excluded.

6.1.2 Septic arthritis

In the analysis of septic arthritis, the same process as with VTE was used, with a combination of data from the NPR and SPDR. However, to further increase the accuracy of the diagnosis, a third process was included; it consisted of a medical record review of all patients with suspected SA following the register analyses. This third process excluded potential remaining false positive cases which consisted of 17 patients (5%). To summarise, if the analysis were to be repeated without the medical record review, an error rate of 5% for detection of SA would be introduced.

6.2 SPECIFIC LIMITATIONS REGARDING THE ANALYSIS OF RISK FACTORS

The risk factor analysis is based mainly on the demographic and perioperative variables included in the SKLR, which are based on the patient's and the surgeon's input. As it is not mandatory to register all variables, a possible selection bias is introduced. Some of the variables, such as BMI, have a large number of missing values and have been addressed specifically in the discussion.

6.2.1 Venous thromboembolism

In the analysis of risk factors for VTE, there is no information regarding previous thrombosis or ongoing oral contraceptive therapy, both known risk factors for VTE. It is thus possible that some patients have an increased risk of VTE, which introduces a bias in the interpretation of the risk factors. However, sex was included in the logistic regression model and no effect on the risk for VTE was demonstrated.

6.2.2 Septic arthritis

The analysis of SA lacks information on specific institutional data, including the preoperative preparation of the patient, equipment and ventilation in the operating room and perioperative routines, factors that could have an effect on the risk of postoperative SA.

The risk factor analysis included variables from the SKLR, as well as variables retrieved from the NPR and SPDR. Information on VTE was retrieved from Study II, but, due to uncertainty regarding causality, the variable was not included in the logistic regression analysis. The variable of diabetes mellitus was based on a proxy: multiple prescriptions of anti-diabetic drugs in the SPDR, a method previously shown to be highly reliable by Rawshani et al. (143).

6.3 SPECIFIC LIMITATIONS REGARDING THE ANALYSIS OF OUTCOME

The analysis of PROMs is limited by the decreasing rate of completed questionnaires for each follow-up occasion, which is taken into consideration by including a non-response analysis.

6.3.1 Non-response analysis

The major limitation in the non-response analysis is that only 17% of the non-respondents were included in the analysis of the KOOS and EQ-5D. This raises concerns about the validity of the results and they can only be assumed to be valid for the whole non-response group.

6.3.2 Subjective outcome after venous thromboembolism

The data on the KOOS and EQ-5D for patients with and without VTE differ substantially in size (55 vs 13,385 for KOOS Pain at one year postoperatively) and the same applies to the confidence intervals. It is possible that only small changes in the PROMs in the group with VTE could alter the findings, which should be taken into account when interpreting the data.

6.3.3 Outcome after septic arthritis

The analyses of outcome after SA have no information on perioperative data at the time of infection. The number of I&Ds performed, together with the properties of the graft, would be valuable information to enable an even better estimate of the impact of the infection. At follow-up, information on return to sport, objective knee function and the possible development of osteoarthritis on X-rays would be valuable information to enable a better understanding and evaluation of the outcome after SA. The analysis of the KOOS and EQ-5D index has shortcomings similar to those in the analysis of subjective outcome after VTE. On the other hand, the group with SA is larger, but the disparity in group size between the group with SA and the group without SA remains.

7 CONCLUSIONS

The general conclusions of this thesis are as follows.

- Using register-based data, analyses of rare complications are possible to achieve.
- The studied complications are rare and in line with previous findings. The incidence of VTE and SA after ACLR are 0.4% and 1.1% respectively.
- The risk factor analysis demonstrated that older age at surgery is the only independent risk factor for VTE after ACLR, whereas male sex, longer operating times, the use of clindamycin instead of cloxacillin and hamstring tendon autografts instead of patellar tendon autografts are all independent risk factors for SA after ACLR.
- Females and older patients have a higher response rate in the SKLR. There are small differences in the KOOS between respondents and non-respondents. The information about the SKLR given to the patient could be improved.
- Patients with VTE after ACLR have a poorer subjective outcome than patients without VTE, which also applies to patients with SA. The analysis of improvement in the KOOS indicates a poorer long-term outcome for patients with SA after ACLR.
- Patients with SA after ACLR run double the risk of revision ACLR as compared to patients without SA.
- The method used in the analysis of incidence of SA confirmed that, wihout using a medical record review, a low rate of misclassification is achievable.

8 POINTS OF PERSPECTIVE

Two rare complications following ACLR are outlined in this thesis and the question of whether they are avoidable remains. The short answer is no, but the risk factor analyses have shown that some parts of patient care are possible to modify, with a probable decrease in the risk of complications.

8.1 VENOUS THROMBOEMBOLISM

The only independent risk factor for VTE was age of 40 years and older, which is a non-modifiable risk factor. What is not answered by the present study is whether thromboprophylaxis should be used. With the already low incidence of VTE and a probable small risk reduction with thromboprophylaxis, a fairly large study population is needed to verify whether or not thromboprophylaxis should be used. The number needed to treat is likely to be high and the side-effects, such as bleeding, must be taken into account. Nevertheless, for the affected patient, the consequences of a VTE can be devastating and it is extremely important to have a well-informed patient before surgery.

Future perspectives on the study of VTE after ACLR could include analyses of oral contraceptives and whether this poses an increased and perhaps modifiable risk of VTE.

8.2 SEPTIC ARTHRITIS

Male sex was an independent risk factor for SA. In the light of the corona pandemic, where male sex is a risk factor for hospital admission and mortality (144, 145), together with previously mentioned studies where male sex is a risk factor for infection following total knee arthroplasty, the question of whether it is the sex per se or whether it is a proxy for an unknown factor remains to be answered.

The modifiable risk factors of operating time, choice of graft and perioperative antibiotics are easier to address. Normally, the surgeon strives to perform the surgery as thoroughly as possible, without unnecessary delays. Increasing the number of surgeries per surgeon, improvements in local routines and fully functional equipment are possible factors that could reduce the operating time.

Graft choice is made with several factors in mind and every type of graft has different advantages and disadvantages. Soaking the graft in vancomycin is a novel method for reducing the incidence of postoperative SA. To date, the published studies have shown promising results with no postoperative infections (146). However, the studies are all retrospective in design, which raises concerns regarding their validity – other unregistered factors that reduce the incidence of SA may have been introduced, together with the introduction of vancomycin. Lastly, the results in this thesis demonstrate that a very low incidence of SA (0.2%) can be achieved without the use of vancomycin.

The choice of perioperative antibiotics is influenced by the presence of allergy to penicillin. As discussed, a more detailed allergy history can reveal the type of allergy and a drug other than clindamycin can safely be used instead.

8.3 OUTCOME

The subjective outcome is affected and reduced by the studied complications. All the analyses of subjective outcome are biased by their low response rates, which the non-response analysis attempted to shed some light upon. It is essential to evaluate the outcome for any administered treatment. Following ACLR, response rates could be improved by better information of the SKLR, and perhaps with user-friendly mobile applications and some kind of feedback of the rehabilitation related to the responses of PROMs.

The risk of revision ACLR is increased among patients who have a postoperative SA. This raises a final interesting question; is revision ACLR in general, associated with infection to a greater extent than shown in this thesis? Recent reports have found bacterial DNA at the time of revision ACLR (147), which could indicate a subclinical infection. This is a finding that raises even more questions and opens up for future research.

9 ACKNOWLEDGEMENTS

I would like to thank everyone who has supported, contributed and encouraged me in the work of this thesis. I would like to express my deepest gratitude to:

Anders Stålman, MD, PhD, my principal supervisor. Thank you for engaging and believing in me, despite the distance with me working at a different hospital. The admission process was not easy, but it now seems that the PhD project is about to be finalised. Without your guidance and immense support, it would not have been possible.

Viktor Lindgren, MD, PhD, my co-supervisor. With a fresh PhD at the time of my admission, you were my principal role model and yet the knowledge gap seemed vast. I am so grateful for your knowledge of the registers and your support during the progression of the PhD project. I believe the knowledge gap nowadays is still there, but it is perhaps somewhat smaller.

Magnus Forssblad, MD, PhD, my co-supervisor, the head of the SKLR. Thank you for your support and never-failing fast replies. Your part in the PhD project is obvious and it would have been difficult to accomplish it without your support.

Per-Mats Janarv, MD, PhD, my co-supervisor, the research group leader at Sports Medicine, MMK, KI. Thank you for your support and ever thoughtful comments. Your suggestions on how to improve the thesis have been most valuable.

Tönu Saartok, MD, PhD, my mentor. Thank you for always showing me how to see things more brightly and having a huge capability for encouraging the people around you.

Anne Garland, MD, PhD, former colleague. Thank you for being supportive and an excellent role model when it comes to initiating a PhD project in the middle of the Baltic Sea, far away from the university and supervisors.

Åke Karlbom, MD, in memoriam, my former colleague and residency programme supervisor. Thank you for guiding me into the world of orthopaedics.

Gunnar Edman, PhD, the statistician. Thank you for helping out with the complex analyses, always with instant replies, no matter what time of the year; and for providing new treats for the Christmas table.

Henrik Hedevik, PhD, the statistician with expert knowledge of the SKLR database. Thank you for your patience with my elementary questions.

Past and present colleagues at the Orthopaedic Departments at Visby Hospital and Skåne University Hospital. Only a few mentioned but certainly no one forgotten.

A special thank you to all colleagues nationwide in Sweden, who assisted me with the medical record review, making Studies III and IV possible.

David Kraus Schmitz, MEng, the grand master of Excel and little brother. Without you, the work in Studies II and III would never have ended.

Marco Kraus Schmitz, MEng, the second little brother and the first language editor. Thank you for your help and support with the English language.

Elin Kurtsdotter, sister-in-law, the master of illustrations. Thank you for helping to make this thesis a bit more enjoyable to read.

Helena Ottosson Kraus, cousin and lawyer. Thank you for proofreading the law section.

Styrbjörn, Emil and **Doris**, the beloved kids. Thank you for reminding me that life is more than the PhD-project.

Johanna, my life companion. Thank you for your (almost) endless support, endurance and encouragement during the work of this thesis.

This thesis was supported by grants provided by Region Gotland, Region Skåne, Skandia, the Swedish Patient Insurance (Regionernas ömsesidiga försäkringsbolag, LÖF) and the Swedish Research Council for Sport Science (Centrum för idrottsforskning, CIF).

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11 APPENDIX

Table 7. ICD-codes

ICD 10-code	*Diagnosis*
I26.0	Pulmonary embolism with mention of acute cor pulmonale
I26.9	Pulmonary embolism without mention of acute cor pulmonale
I80.0	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
I80.8	Phlebitis and thrombophlebitis of other sites
I80.9	Phlebitis and thrombophlebitis of unspecified site
I82.8	Embolism and thrombosis of other specified veins
I82.9	Embolism and thrombosis of unspecified vein
M00	Pyogenic arthritis
T84	Complication of internal orthopaedic devices, implants and graft

ICD, International Classification of Disease

Table 8. ATC code, type of antibiotic and dosage used in the selection process.

ATC code	*Antibiotic*	*Daily dose*
J01CA04	Amoxicillin	750 mg 1x3
J01CR02	Amoxicillin and clavulanic acid	500/125 mg 1x3
		875/125 mg 1x2
J01DB05	Cefadroxil	500 mg 1x2
		1 g 1x2
J01MA02	Ciprofloxacin	250 mg 2x2
		500 mg 1x2
		750 mg 1x2
J01CE02	Phenoxymethylpenicillin	1 g 2x3
J01CF05	Flucloxacillin	500 mg 2x3
		750 mg 2x3
		1g 1x3
J01XC01	Fusidic acid	250 mg 2x3
J01FF01	Clindamycin	150 mg 1x3
		300 mg 1x3
J01MA12	Levofloxacin	500 mg 1x1
J01XX08	Linezolid	600 mg 1x2
P01AB01	Metronidazole	400 mg 1x3
J01MA14	Moxifloxacin	400 mg 1x1
J04AB02	Rifampicin	600 mg 1x1
J01EE01	Sulfamethoxazole and trimethoprim	80/400 mg 2x2
		160/800 mg 1x2

ATC, Anatomical Therapeutic Chemical

Table 9. Descriptive data of the VTE and non-VTE group.

	All patients			*Patients without thromboprophylaxis*			*Patients with thromboprophylaxis*		
	VTE n=95	*non-VTE n=25,919*	*P Value*	*VTE n=59*	*non-VTE n=16,494*	*P Value*	*VTE n=36*	*non-VTE n=9425*	*P Value*
Patient demographics									
Female, n (%)	36 (37.9)	11,037 (42.6)	0.356	22 (37.3)	6591 (40.0)	0.676	14 (38.9)	4446 (47.2)	0.320
Male, n (%)	59 (62.1)	14,882 (57.4)		37 (62.7)	9903 (60.0)		22 (61.1)	4979 (52.8)	
Smoker, n (%)	2 (3.7)	748 (6.0)	0.771	0 (0.0)	521 (6.2)	0.259	2 (8.7)	227 (5.6)	0.372
Non-smoker, n (%)	52 (96.3)	11,758 (94.0)		31 (100.0)	7922 (93.8)		21 (91.3)	3836 (94.4)	
Mean age at surgery, yrs (range)	31.4 (15-55)	26.8 (7-74)	<0.001	32.0 (15-55)	27.0 (7-74)	<0.001	30.5 (16-51)	26.5 (10-64)	0.015
Normal BMI (<25 kg/m²), n (%)	28 (84.8)	7573 (91.1)	0.211	16 (88.9)	5185 (92.2)	0.647	12 (80.0)	2388 (88.9)	0.229
Obese BMI (≥ 30 kg/m²), n (%)	5 (15.2)	737 (8.9)		2 (11.1)	439 (7.8)		3 (20.0)	298 (11.1)	
Perioperative data									
Revision surgery, n (%)	6 (6.3)	1613 (6.2)	0.970	3 (5.1)	1058 (6.4)	>0.999	3 (8.3)	555 (5.9)	0.469
Primary surgery, n (%)	89 (93.7)	24,306 (93.8)		56 (94.9)	15,436 (93.6)		33 (91.7)	8870 (94.1)	
Meniscal repair, n (%)	10 (10.5)	1761 (6.8)	0.149	5 (8.5)	1243 (7.5)	0.802	5 (13.9)	518 (5.5)	0.046
No meniscal repair, n (%)	85 (89.5)	24,158 (93.2)		54 (91.5)	15,251 (92.5)		31 (86.1)	8907 (94.5)	
Outpatient surgery, n (%)	82 (86.3)	19,873 (76.7)	0.026	50 (84.7)	12,962 (78.6)	0.249	32 (88.9)	6911 (73.3)	0.035
Inpatient surgery, n (%)	13 (13.7)	6046 (23.3)		9 (15.3)	3532 (21.4)		4 (11.1)	2514 (26.7)	
Operating time, min (SD)	71.9 (20.7)	74.8 (25.7)	0.189	69.0 (18.7)	72.1 (25.4)	0.217	77.0 (23.2)	79.5 (25.6)	0.571
Choice of graft									
Patellar tendon, n (%)	4 (4.4)	1942 (7.6)	0.400	3 (5.4)	1040 (6.4)	0.741	1 (2.9)	902 (9.6)	0.515
Hamstring tendon, n (%)	87 (95.6)	23,276 (90.8)		53 (94.6)	14,890 (91.6)		34 (97.1)	8386 (89.3)	
Allograft, n (%)	0 (0.0)	142 (0.6)		0 (0.0)	105 (0.6)		0 (0.0)	37 (0.4)	
Other, n (%)	0 (0.0)	281 (1.1)		0 (0.0)	214 (1.3)		0 (0.0)	67 (0.7)	

VTE, venous thromboembolism; BMI, body mass index; SD, standard deviation;

Table 10. KOOS for each subscale presented preoperatively and at two-years postoperatively for respondents and late respondents with mean and 95% confidence intervall.

		KOOS subscales				
		Symptoms	Pain	ADL	Sport/Rec	QoL
Respondents	Pre op.	70.5(69.6-71.6)	75.1(74.2-76.1)	83.3(82.4-84.3)	40.6(39.3-42.2)	33.8(32.9-34.9)
	Two yrs	77.8(76.8-78.8)	84.5(83.6-85.4)	91.1(90.4-91.9)	65.3(63.8-66.8)	59.9(58.5-61.1)
Late Respondents	Pre op.	70.6(68.4-72.8)	74.9(72.5-76.7)	84.1(81.8-85.9)	43.5(39.9-46.2)	33.2(30.7-35.2)
	Two yrs	74.8(72.7-77.0)	81.2(79.2-83.1)	89.1(87.4-90.6)	62.5(59.1-65.5)	55.8(53.2-58.9)

ADL, activity of daily life; Sport/rec, sport and recreational function; Qol, knee-related quality of life

Table 11. EQ5D index and EQ5D VAS presented preoperative and at two-years for respondents and late respondents with mean and 95% confidence intervall.

		EQ5D subscales	
		Index	VAS
Respondents	Pre op.	0.68 (0.67-0.70)	61.4 (60.1-62.8)
	Two yrs	0.81 (0.80-0.82)	75.9 (74.8-76.9)
Late Respondents	Pre op.	0.66 (0.63-0.69)	62.1 (58.9-64.8)
	Two yrs	0.79 (0.77-0.82)	75.4 (72.8-77.7)

VAS, visual analogue scale

Table 12. Mean scores of the KOOS and EQ5D subscales for patients with and without venous thromboembolism. Scores are presented preoperatively and at one and two years postoperatively. Data is adjusted for age.

		VTE		Non-VTE		P Value
		n	Mean score (95% CI)	n	Mean score (95% CI)	
KOOS Symptoms	pre-op	68	67.5 (63.1-71.9)	17,542	70.0 (69.7-70.3)	0.267
	one yr	55	64.2 (59.3-69.0)	13,385	76.4 (76.1-76.8)	< 0.001
	two yrs	39	72.2 (66.5-78.0)	11,799	77.6 (77.2-77.9)	0.069
KOOS Pain	pre-op	68	72.9 (68.7-77.1)	17,543	74.6 (74.4-74.9)	0.419
	one yr	55	74.8 (70.4-79.1)	13,385	83.6 (83.4-83.9)	< 0.001
	two yrs	39	79.1 (73.9-84,3)	11,801	84.0 (83.7-84.3)	0.062
KOOS ADL	pre-op	68	82.3 (78.3-86.3)	17,541	83.7 (83.4-83.9)	0.509
	one yr	55	82.5 (78.8-86.2)	13,384	90.7 (90.4-90.9)	< 0.001
	two yrs	39	85.9 (81.4-90.3)	11,800	90.8 (90.5-91.0)	0.030
KOOS Sport/Rec	pre-op	68	39.7 (33.2-46.1)	17,543	41.2 (40.8-41.6)	0.641
	one yr	55	49.8 (42.4-57.2)	13,385	63.2 (62.8-63.7)	< 0.001
	two yrs	39	55.3 (46.6-64.1)	11,799	64.3 (63.8-64.8)	0.046
KOOS QoL	pre-op	68	33.6 (29.1-38.1)	17,542	33.6 (33.3-33.9)	0.999
	one yr	55	45.3 (38.8-51.8)	13,387	57.9 (57.5-58.4)	< 0.001
	two yrs	39	51.9 (44.2-59.6)	11,800	59.6 (59.1-60.0)	0.051
EQ5D Index	pre-op	65	0.66 (0.60-0.72)	16,442	0.68 (0.67-0.68)	0.687
	one yr	51	0.67 (0.61-0.73)	12,895	0.79 (0.78-0.79)	< 0.001
	two yrs	38	0.79 (0.72-0.85)	11,359	0.80 (0.80-0.80)	0.641
EQ5D VAS	pre-op	64	60.2 (54.5-65.9)	16,262	62.7 (62.4-63.1)	0.385
	one yr	53	63.9 (58.4-69.3)	12,805	75.1 (74.8-75.5)	< 0.001
	two yrs	38	71.1 (64.7-77.5)	11,489	76.0 (75.6-76.3)	0.139

VTE, venous thromboembolism; CI, confidence interval; ADL, activity of daily living; Sport/rec, sport and recreational function; QoL, knee-related quality of life; VAS, visual analogue scale

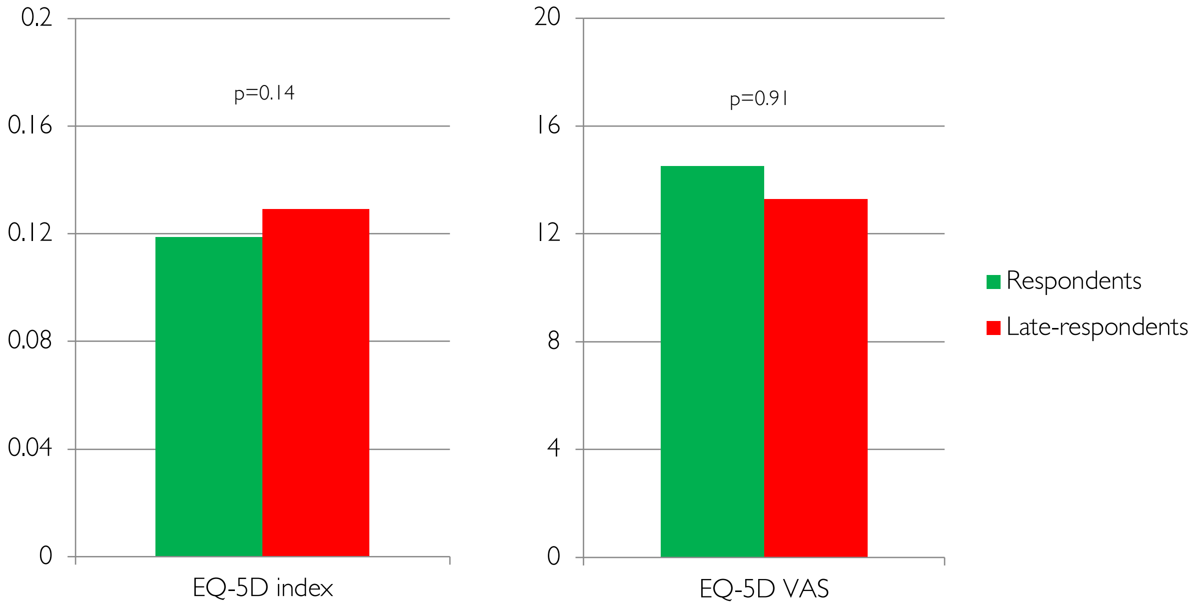

Figure 15. The improvement of EQ-5D from preoperatively to two-year follow-up presented for each subscale for respondents and late-respondents. Data adjusted for age at surgery and sex.
VAS, visual analogue scale

Table 13a. Demographic and clinical characteristics of patients with (n=291) and without (n=25,018) septic arthritis.

		Septic Arthritis		
Variable, (incidence of SA)		Yes	No	p-value
Sex	*total n*	25,309		
Woman, (0.8%)	*n (%)*	91 (31.3)	10,697 (42.8)	<0.001
Man, (1.4%)	*n (%)*	200 (68.7)	14,321 (57.2)	
Age at surgery	*total n*	25,309		
in years	*M (range)*	27.2 (11-53)	26.8 (7-67)	0.556
Body Mass Index, BMI	*total n*	11,904		
	M (SD)	25.4 (3.94)	24.5 (3.52)	0.003
Normal weight (BMI<25), (0.9%)	*n (%)*	71 (54.6)	7425 (63.1)	0.132
Overweight (BMI 25-30), (1.4%)	*n (%)*	53 (40.8)	3857 (32.8)	
Obese (BMI >30), (1.2%)	*n (%)*	6 (4.6)	483 (4.1)	
Smoking	*total n*	12,169		
Yes, (0.8%)	*n (%)*	6 (4.5)	713 (5.9)	0.504
No, (1.1%)	*n (%)*	126 (95.5)	11,324 (94.1)	
Diabetes Mellitus	*total n*	25,309		
Yes, (1.1%)	*n (%)*	2 (0.7)	187 (0.7)	>0.999
No, (1.2%)	*n (%)*	289 (99.3)	24, 831 (99.3)	
VTE	*total n*	25,309		
Yes, (4.4%)	*n (%)*	4 (1.4)	87 (0.3)	0.021
No, (1.1%)	*n (%)*	287 (98.6)	24,391 (99.7)	

M, mean; SD, standard deviation

Table 13b. Perioperative data of patients with (n= 291) and without (n= 25,018) septic arthritis.

		Septic Arthritis		
Variable, (incidence of SA)		*Yes*	*No*	*p-value*
Type of surgery	*total n*	25,309		
Outpatient surgery, (1.2%)	*n (%)*	232 (79.7)	19,130 (76.5)	0.192
Inpatient surgery, (1.0%)	*n (%)*	59 (20.3)	5888 (23.5)	
Type of surgery	*total n*	25,309		
Primary, (1.2%)	*n (%)*	276 (94.8)	23,622 (94.4)	0.753
Revision, (1.1%)	*n (%)*	15 (5.2)	1396 (5.6)	
Cartilage lesion	*total n*	25,309		
Yes, (1.4%)	*n (%)*	99 (34.0)	6780 (27.1)	0.008
No, (1.0%)	*n (%)*	192 (66.0)	18,238 (72.9)	
Meniscal suture	*total n*	25,309		
Yes, (1.2%)	*n (%)*	7.2 (21.0)	1668 (6.7)	0.709
No, (1.1%)	*n (%)*	270 (92.8)	23,350 (93.3)	
Choice of graft	*total n*	25,309		
Hamstring tendon, (1.2%)	*n (%)*	280 (96.2)	23,083 (92.3)	0.012
Patellar tendon, (0.6%)	*n (%)*	11 (3.8)	1935 (7.7)	
Operating time in min	*total n*	23,919		
	M (Range)	82.0 (35-246)	74.5 (17-304)	<0.001
<70 min, (0.8%)	*n (%)*	84 (30.4)	10,631 (45.0)	<0.001
≥70 min, (1.5%)	*n (%)*	192 (69.6)	13,012 (55.0)	
Perioperative antibiotic	*total n*	24,744		
Cloxacillin, (1.1%)	*n (%)*	272 (94.8)	23,861 (97.6)	0.002
Clindamycin, (2.5%)	*n (%)*	15 (5.2)	596 (2.4)	
Perioperative antibiotic, dose	*total n*	25,309		
1 dose, (1.2%)	*n (%)*	193 (66.3)	16,280 (65.1)	0.657
2 or more doses, (1.1%)	*n (%)*	98 (33.7)	8738 (34.9)	
Prolonged antibiotic prophylaxis	*total n*	25,309		
Yes, (0.7%)	*n (%)*	12 (4.1)	1638 (6.5)	0.101
No, (1.2%)	*n (%)*	279 (95.9)	23,392 (93.5)	

M, mean

Table 14. Anticoagulants used for definition of VTE.

Generic name	*ATC code*	*Minimum daily dosage*
Dalteparin	B01AB04	10,000 IU
Enoxaparin	B01AB05	8000 IU
Rivaroxiban	B01AF01	30 mg
Tinzaparin	B01AB10	8000 IU
Warfarin	B01AA03	-

ATC, Anatomic Therapeutic Chemical; IU, International Unit